Molecular Modeling in Undergraduate Chemical Education

Summer 2005

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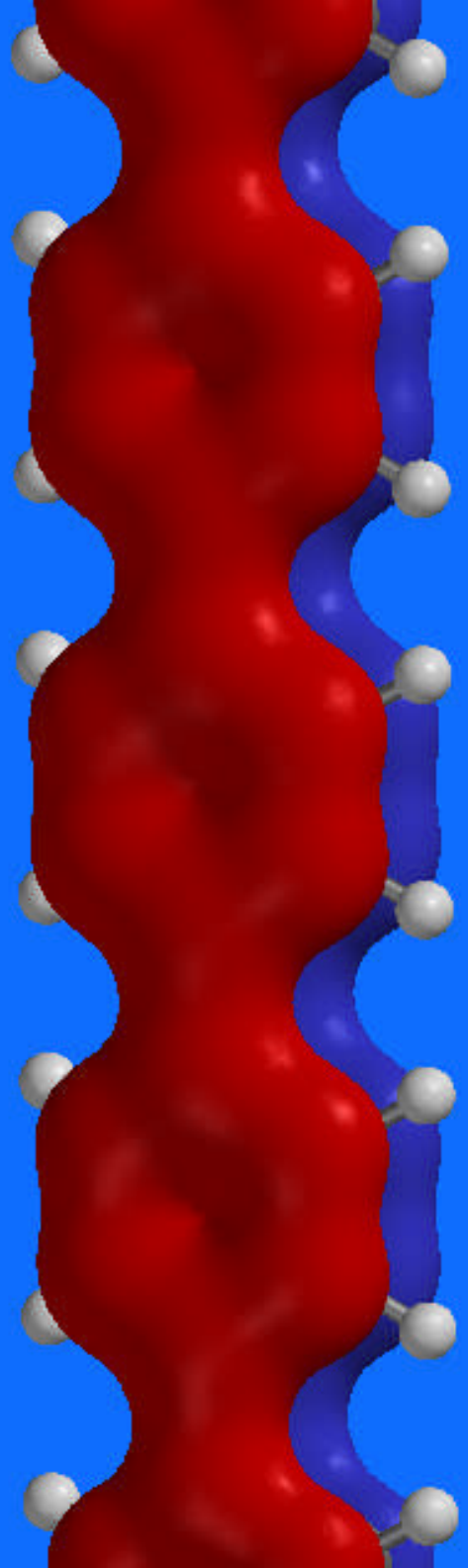


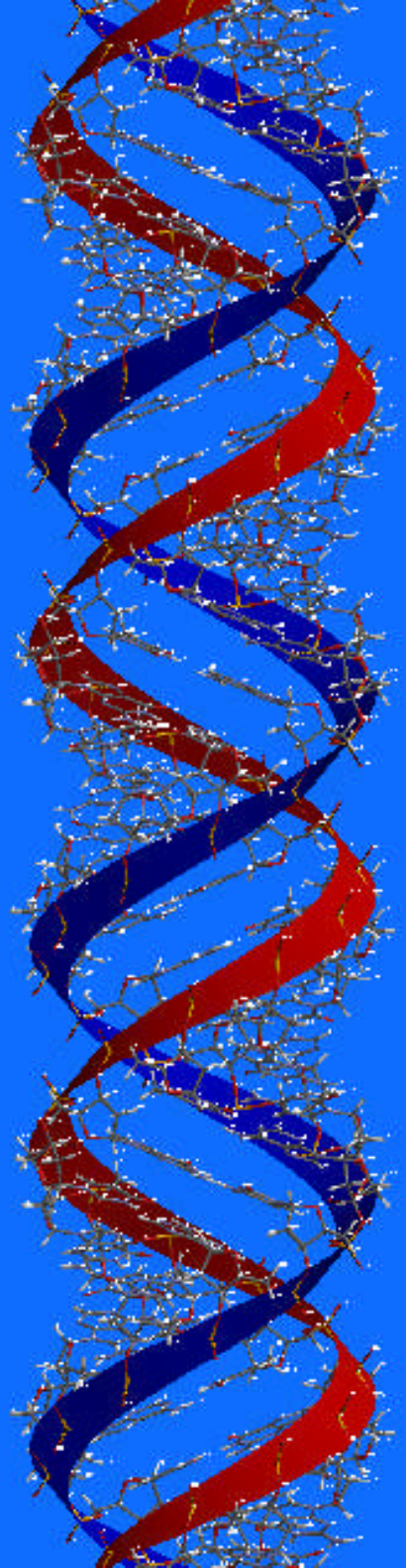
A Workshop featuring

Spartan

for Windows, Linux, Unix and Mac

A World of Molecular Visualization Possibilities!

WAVEFUNCTION



What are we going to do today?

- Introduce you to molecular modeling with Spartan software and show how you can use this in teaching
- Give you plenty of time to have fun working with the software
- Demonstrate the Cambridge Crystal Structure Database (CCSD) and its interface with Spartan
- Introduce *Odyssey*, the new Wavefunction courseware
- Exchange ideas
- Address your needs

The Plan

Part I

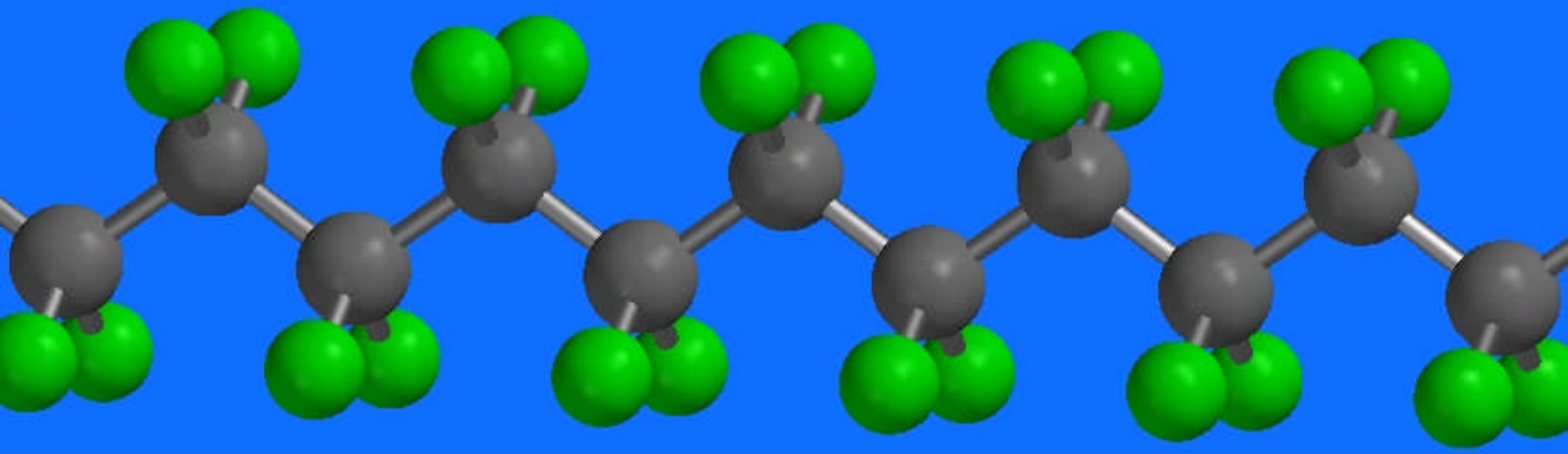
- Introduction to modeling and Spartan
- Build some molecules
- Overview of computational chemistry
- An examination of PABA
- Lunch

Part II

- Discussion of Odyssey, SpartanModel, and Spartan Student Edition
- Hands-on with Odyssey
- Animations in Spartan
- Modeling reaction chemistry
- Stump the band

What we won’t do today

- Overwhelm you
- Teach you the full intricacies of Spartan
- Teach you all about computational chemistry



What can you do with molecular modeling in your classroom and laboratory?

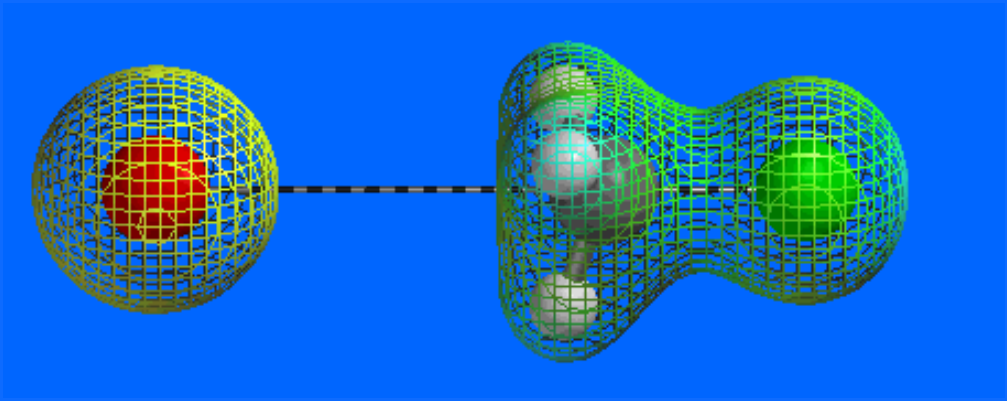
- Enhance teaching of selected concepts and content
- Move from two dimensions into three
- Chemistry is about molecules, and the behavior of electrons
- Prepare course material and WWW images
- Computational experiments in place of selected wet labs
- Motivate students to be excited about chemistry
- Research, enrichment and special projects
- Advanced courses
- Better prepare students for graduate school and careers

The Modeling Experiment

- ***Build Structures***
  Spartan allows the rapid construction of virtually any structure in three dimensions.
- ***Perform Calculations***
  Classical and quantum mechanical models offer sophisticated descriptions of both known and hypothetical molecules.
- ***Visualize and Interpret Results***
  Data includes structure, energies, molecular orbitals, electron densities, vibrational modes. These can be displayed as surfaces or animations.

What the Modeling Experiment Can Provide:

- Optimized Structures
- Electronic Properties
- Spectra
- Reactivity
- Reactions and other Animations



Building Molecules in Spartan

Spartan Architecture

Construction
Entry Mode
Expert Mode
Peptide Builder
Nucleotide Builder

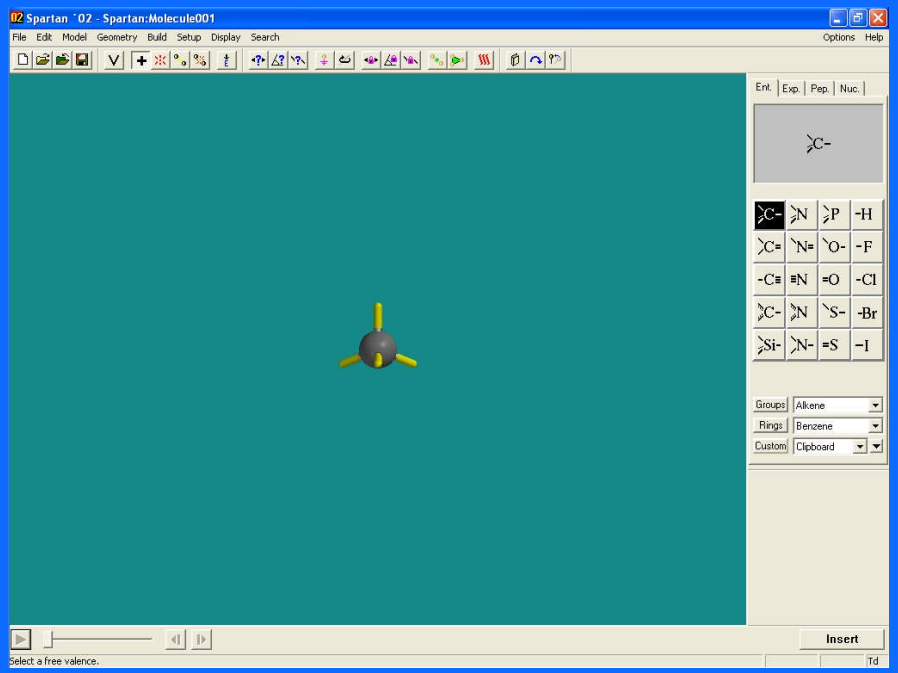
Computation
Molecular Mechanics
ab Initio
Semi-empirical
Density Functional Theory
Other methods

Graphical User Interface

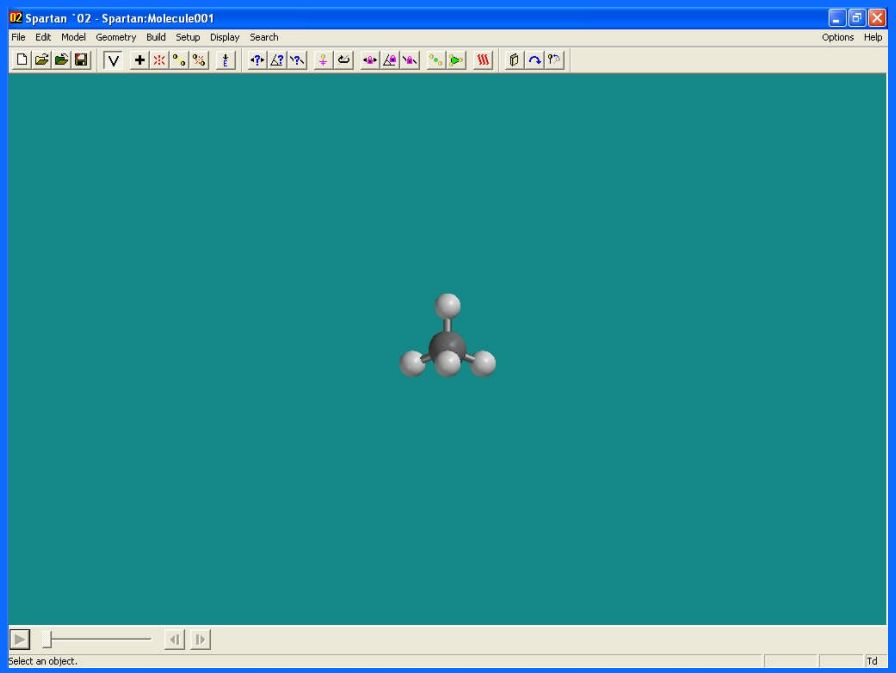
Visualization
Various display modes
Properties
Surfaces
Animations

Exportation
Spartan exchange format
Other molecule formats
Images
Movies

A Tale of Two Modes



BUILDER Mode

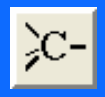


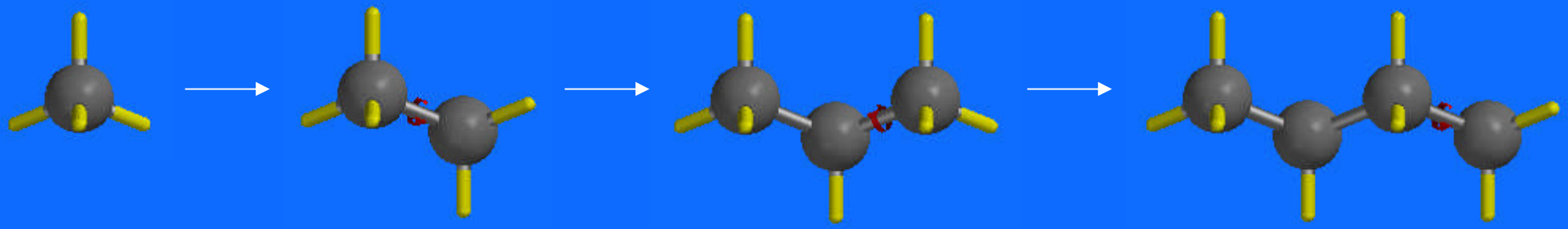
VIEWER Mode

Enough chatter…

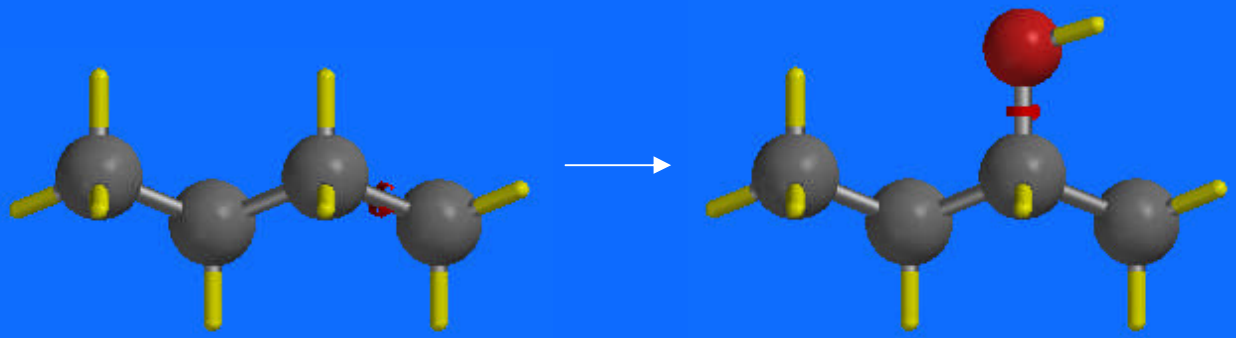
Let’s Build Some Molecules!

sec-Butanol

1) On the Entry palette, select a tetrahedral carbon 
and build a chain of four carbon atoms



2) Select a bent oxygen 
and add it to an interior carbon of the chain

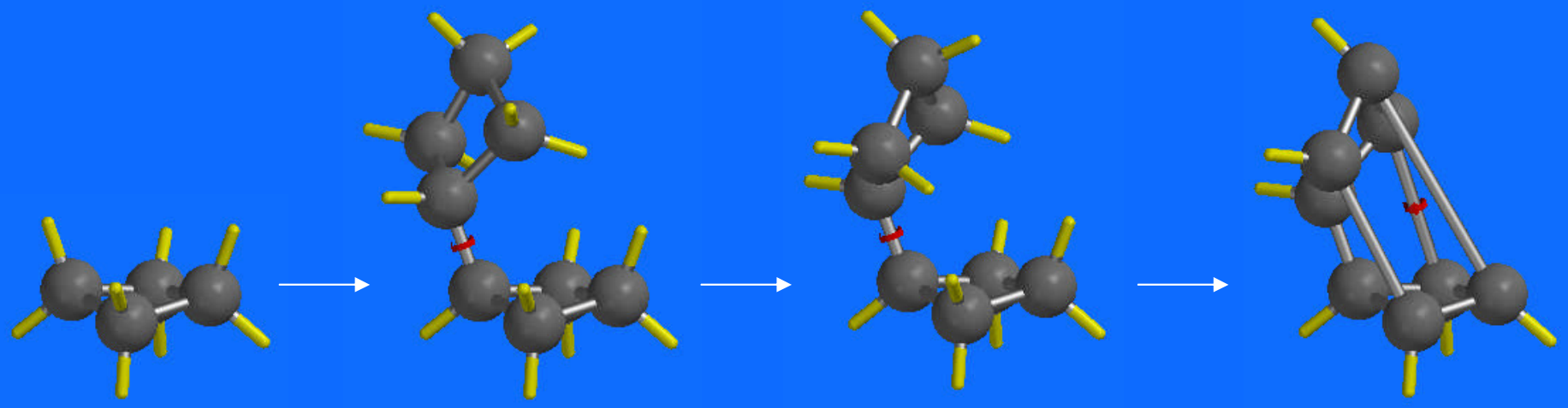


Selected bonds can be rotated with the ALT key and left mouse button.
Also try the Minimizer  and examine various Model types

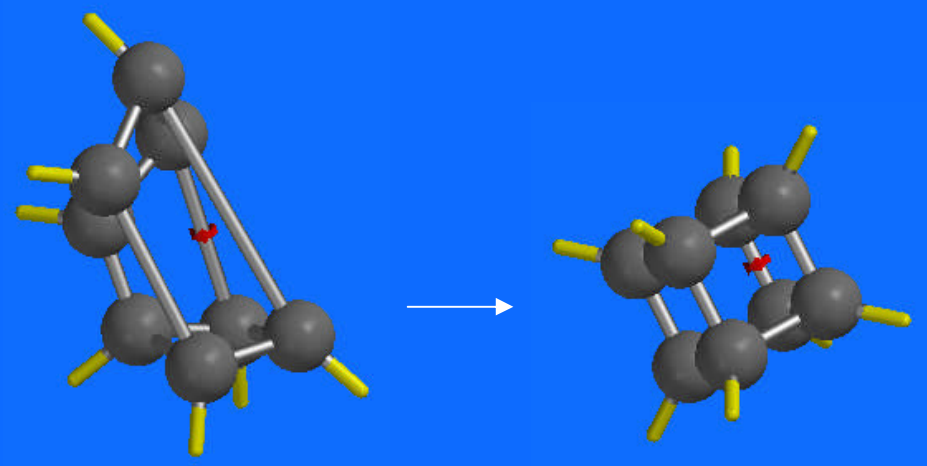
By the way… *What is its chirality?*

Cubane

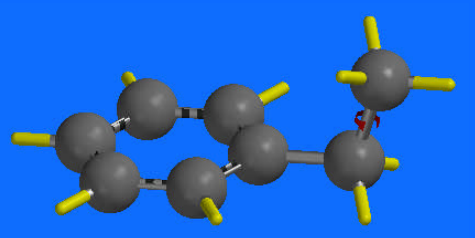
1) Choose Cyclobutane from the Rings menu, then attach a second to the first. Rotate the second ring until it eclipses the first. Use Make Bond to connect the carbons.



2) Minimize the structure.



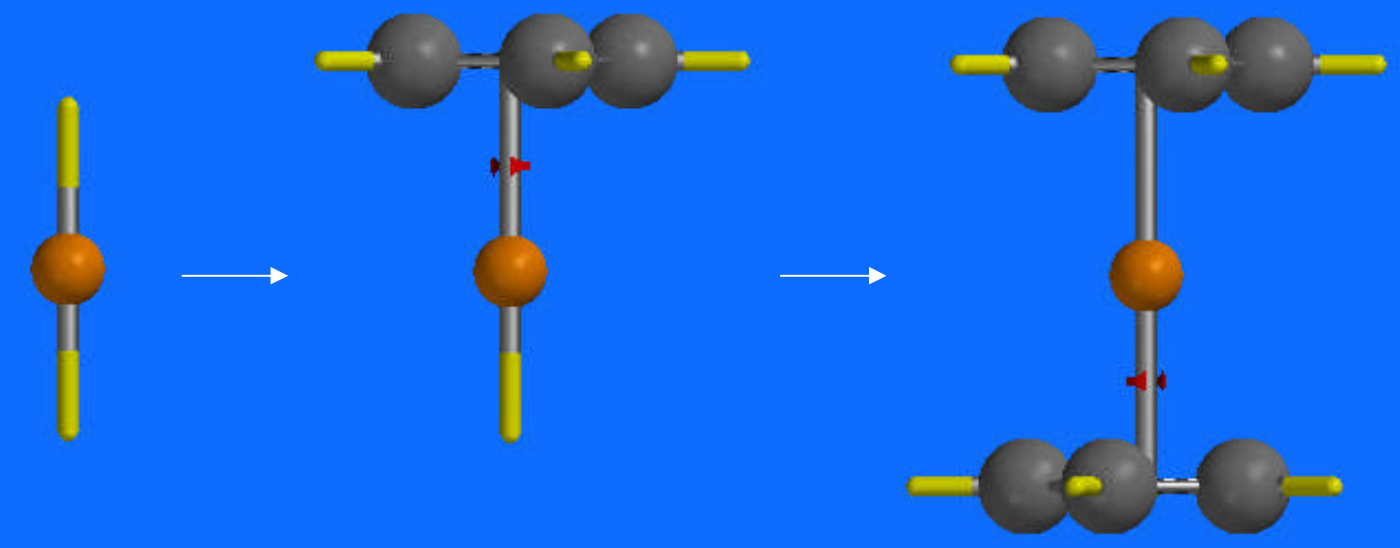
Polystyrene



1) Create a molecule of ethylbenzene.
2) Holding down both mouse buttons, drag a box around the molecule, and select Copy from the Edit menu.
3) Click on the Custom button in the Entry palette, and choose Clipboard from the menu.
4) In the fragment window, select the attachment point.
5) Attach monomers to desired length.

Ferrocene (a molecular sandwich)

1) On the Expert palette, choose Fe and a linear bonding pattern Fe
2) Choose Cyclopentadienyl from the Ligands menu, and attach one to each open valence of the iron. Then Minimize!



Building Biomolecules

Polypeptides

DNA & RNA

A little bit about theory……

Classical Mechanics

Molecular Mechanics based on Force Field Methods
(MM2, MM3, Amber, Sybyl, UFF etc.)

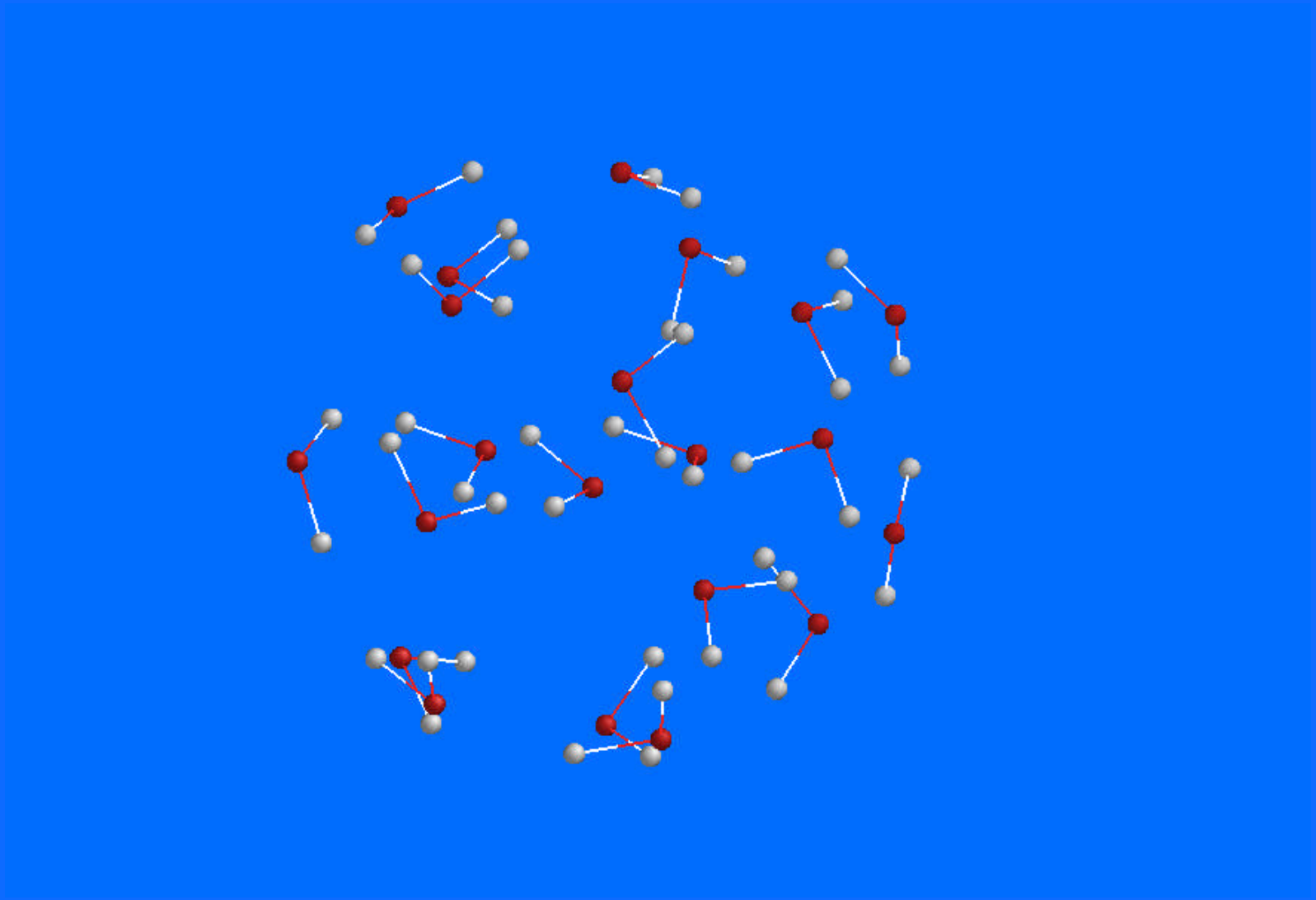
Based on Hooke's law, van der Waals interactions, electrostatics etc., and parameterized to fit experimental data.

This method considers a molecule as a collection of balls (atoms) and springs (bonds). Newtonian physics is employed to determine structures and energies.

However, calculations cannot be performed without knowing some *parameters:* force constants, bond lengths and angles, torsions angles, etc. These parameters are based upon the best fit to experimental results.

The collection of equations and parameters is called a “force field” -- not to be confused with something Captain Kirk would encounter.

Hydrogen bonding is easily illustrated by modeling a set of water molecules with molecular mechanics



Quantum Mechanics

$$\hat{H}\psi = E\psi$$

If we could find an exact solution for the Schrödinger equation of a molecular system, we would know everything there is to know about that system.

But we can't.

At least, not *exactly*…

Basis Sets for Computational Models

Approximate Solutions to the Schrödinger equation

increasing accuracy, but also increasing demands

Semi-Empirical Methods

- Uses Slater type functions (combinations of Gaussian functions)
- Considers only valence electrons and parameterized to fit experimental results from known systems to greatly lessen computational demands

- AM1 Useful for upper main group elements and Zn
- PM3 Useful for main group elements and transition metals
- MNDO Useful for many main group elements and Zn group

Ab Initio (Hartree-Fock) Methods

- Non–empirical; from "first principles"
- based on the Hartree-Fock self-consistent field (HF-SCF) method using Gaussian functions
- includes all electrons and uses minimal approximation
- large collection of methods and levels of theory
- increase in complexity for both basis functions and electron correlation

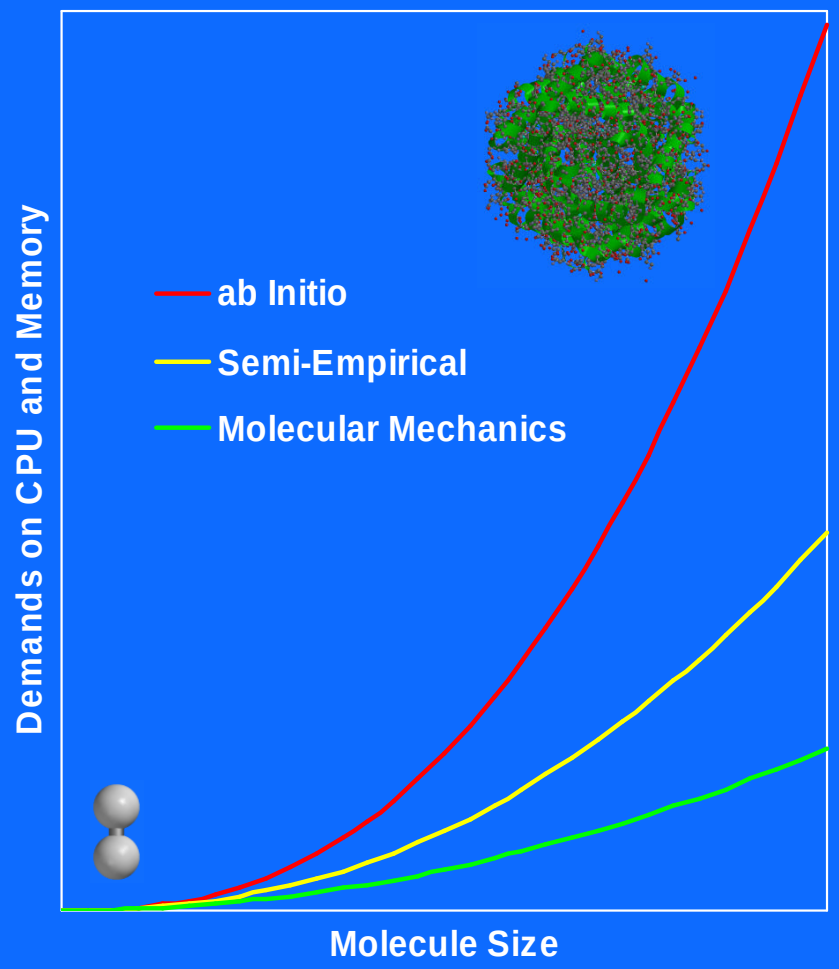
• STO-3G	Minimal basis set	unreliable energetics
• 3-21G(*)	Split-valence / Double Zeta	excellent results
• 6-31G*	Polarized basis sets	highly accurate
• 6-311+G**	Extended basis sets	highly accurate
• Hartree-Fock limit:	infinite basis set	

Density Functional Methods

- Based on electron density; includes electron correlation.

As with any instrumental method…

Choose your method wisely, and interpret your results with care



Molecular Mechanics

- Cannot explore electronic structural features
- Can do a wide range of molecules
- Parameter dependent

Semi-Empirical

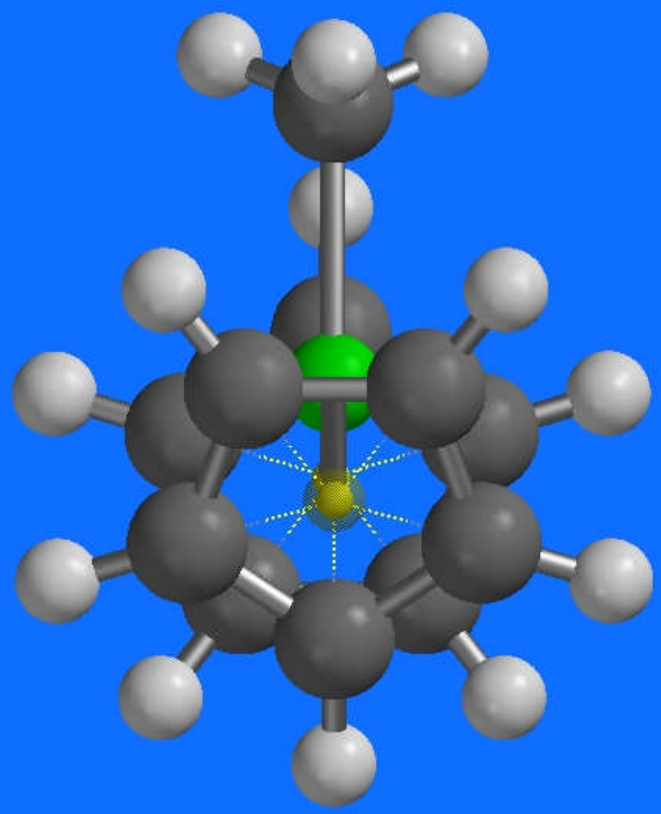
- Wide range of structures
- Relatively fast
- Electronic based
- But can be less reliable…

ab initio

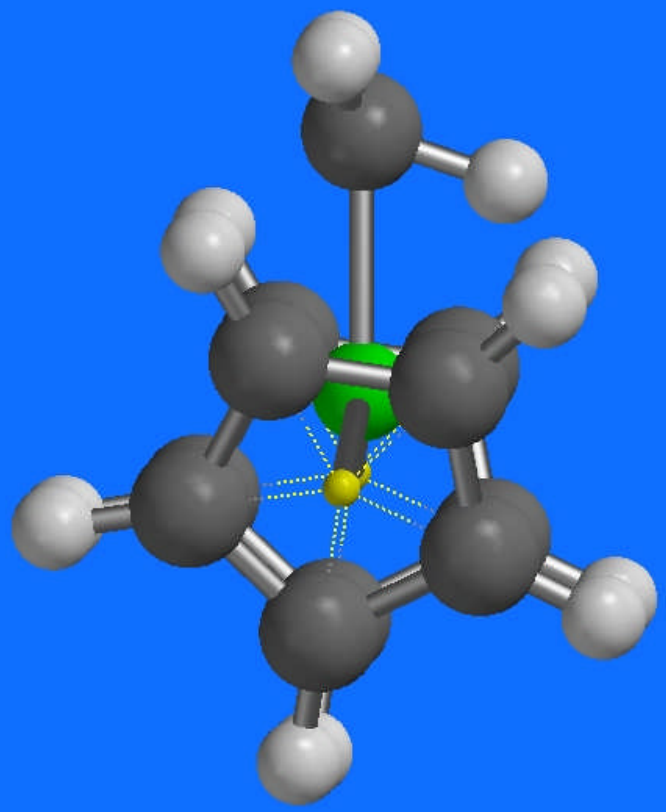
- Interesting chemistry
- Electronic details
- Reactive intermediates, Transition states, and Reaction pathways
- Computationally demanding

Classical vs. Quantum Mechanics

$[Cp_2TiMe]^+$ and the Agostic Interaction



MMFF



PM3 Semi-Empirical

A Comparison of Tasks

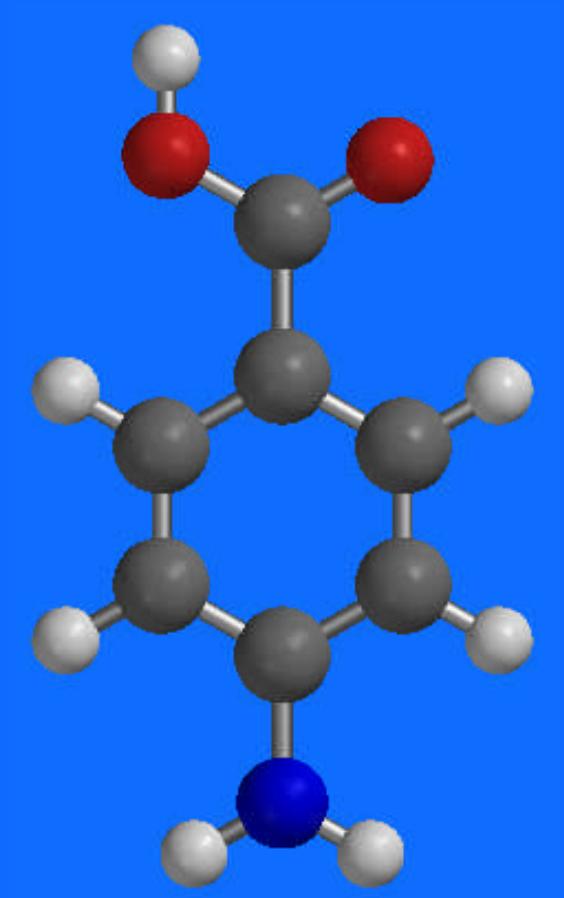
TASK	MM	SE	HF	DFT	MP2
Geometry (organic)	C	G	G	G	G
Geometry (metals)		G	P	G	P
Geometry (transition state)		C	G	G	G
Conformation	G	P	G	G	G
Thermochemistry (general)		P	C	G	G
Thermochemistry (isodesmic*)		P	G	C	G
COST	low →				high

G	Good
C	with Caution
P	Poor

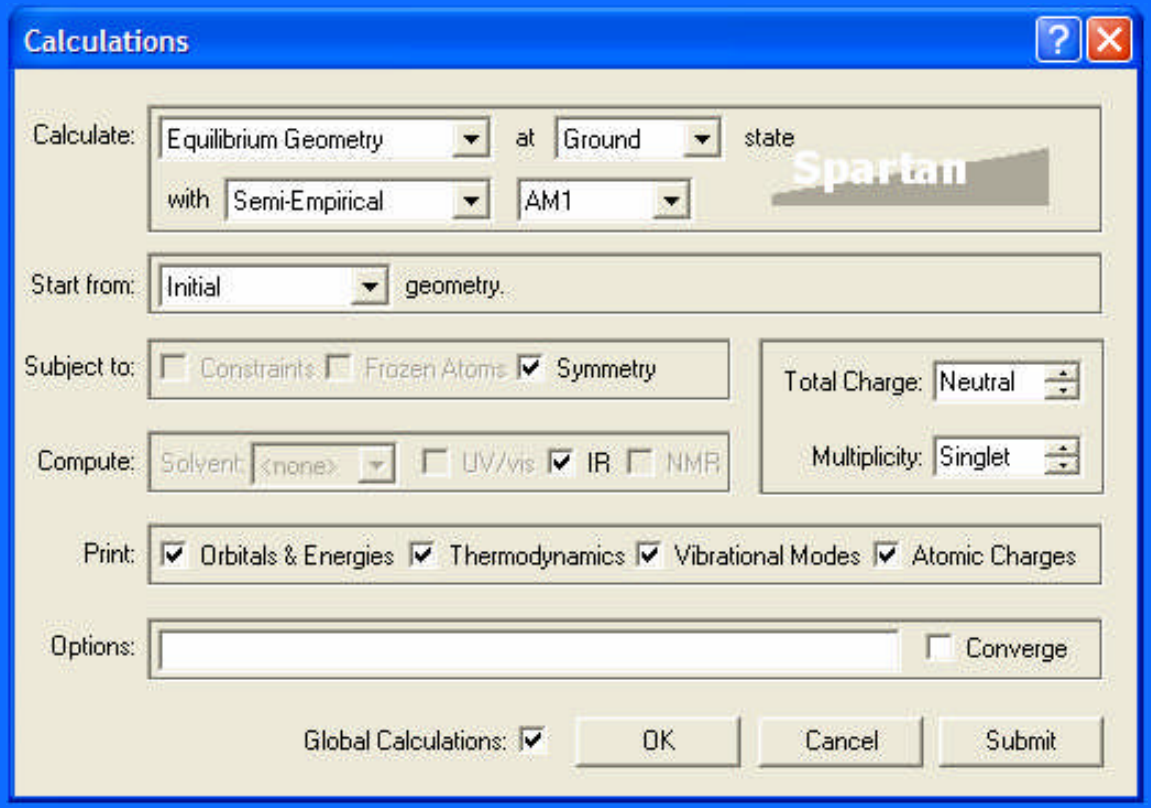
* chemical changes in which there is retention of the number of bonds of a given formal type, but with a change in their relation to one another

Let’s Examine a Molecule

PABA –
p-Aminobenzoic Acid



Setup a Calculation



- **Calculate: *Equilibrium Geometry* at *Ground* state**
- **with: *Semi-Empirical* method *AM1***
- **Start from: *Initial* geometry**
- **Subject to: *Symmetry***
- **Compute: *IR***
- **Print: choose all**
- **Options: none**
- **Total Charge: *Neutral***
- **Multiplicity: *Singlet***
- **Click on *Submit***

While the calculation is running, you can check its progress using the Monitor in the Options menu

Measure the Molecule

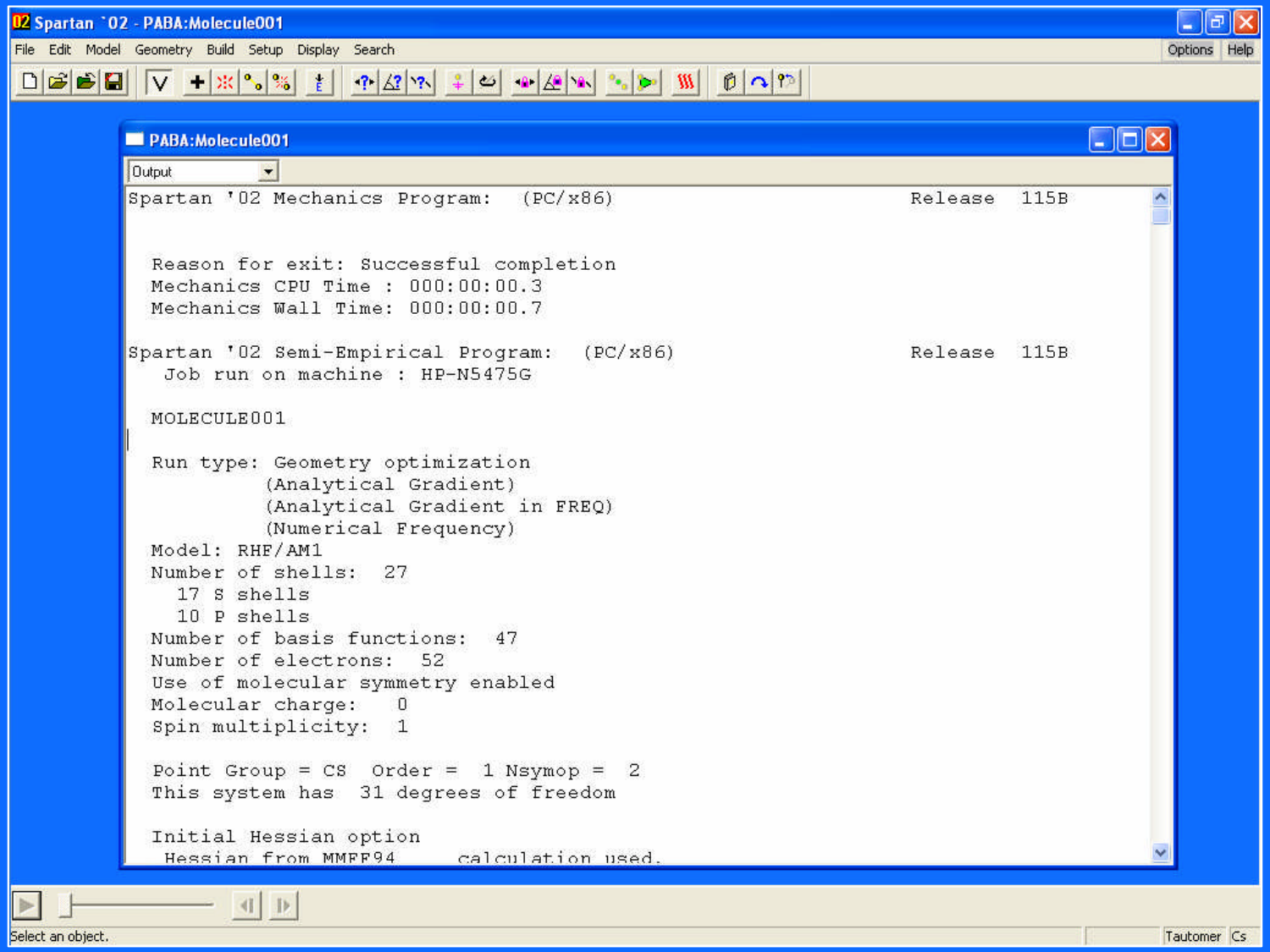
Use these buttons to measure

 Bond Lengths

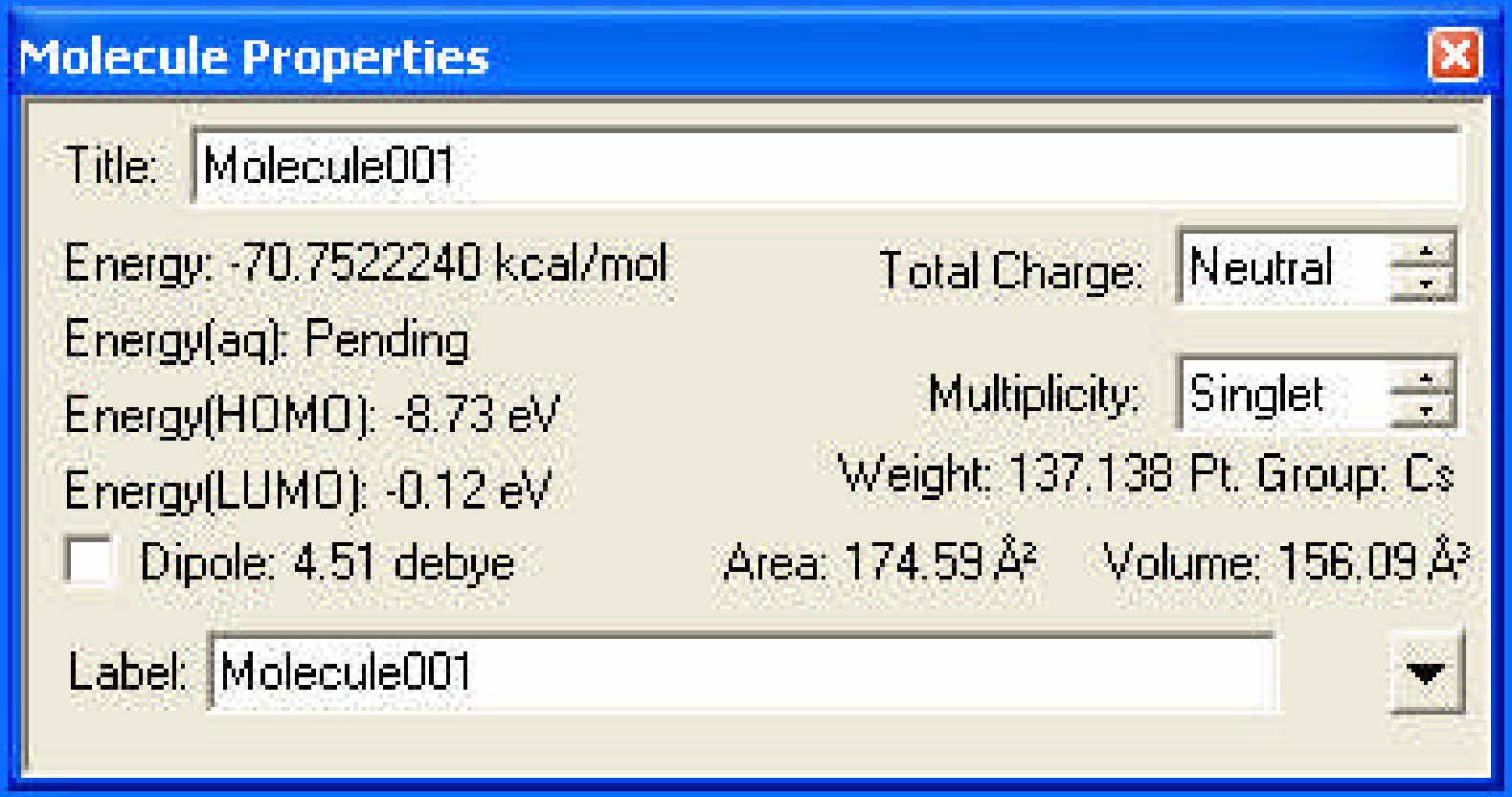
 Bond Angles

 Dihedral Angles

Display Output



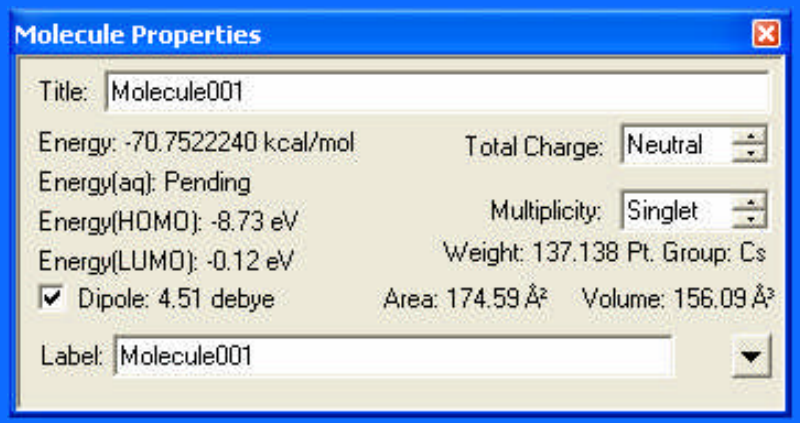
Display Properties

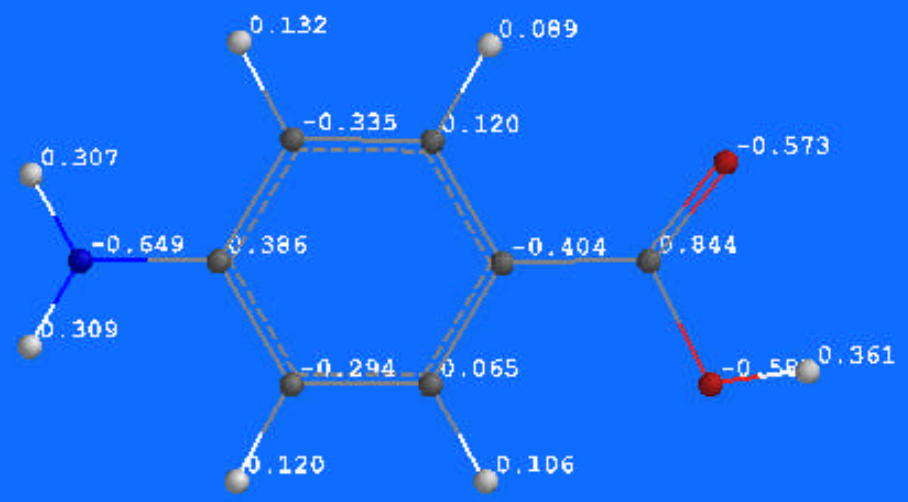


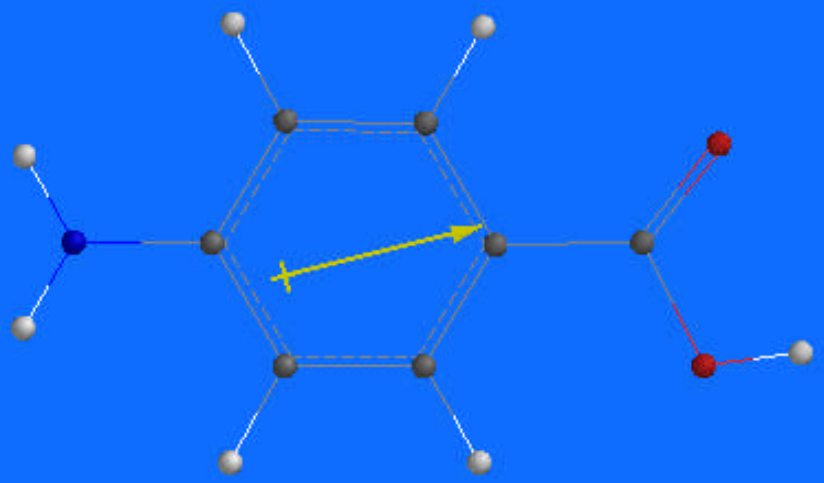
Electrostatic charges and dipole moment show the polarization of PABA

In the Model menu, choose Labels, then choose Configure and select the type of charge to indicate.

Turn on a Dipole vector from the Display Properties box.

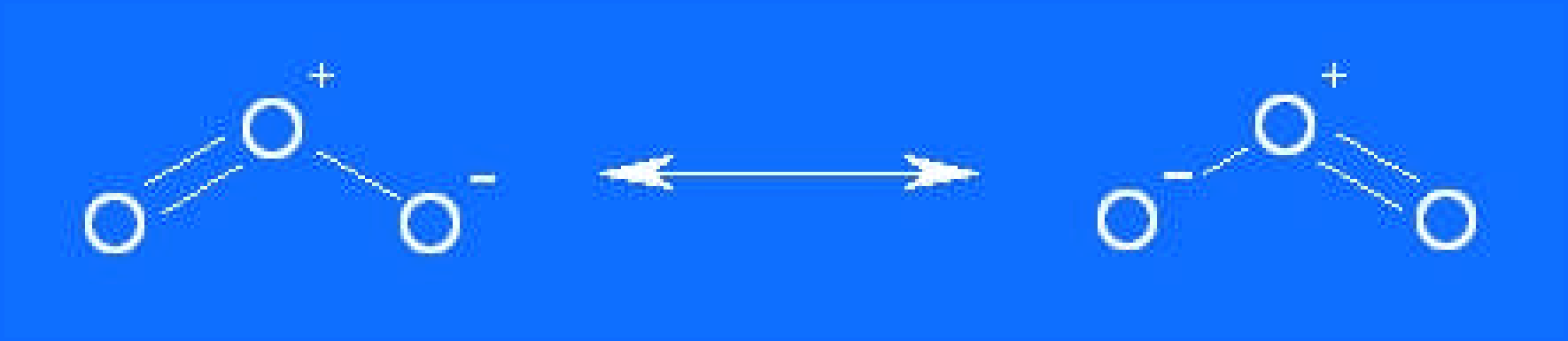


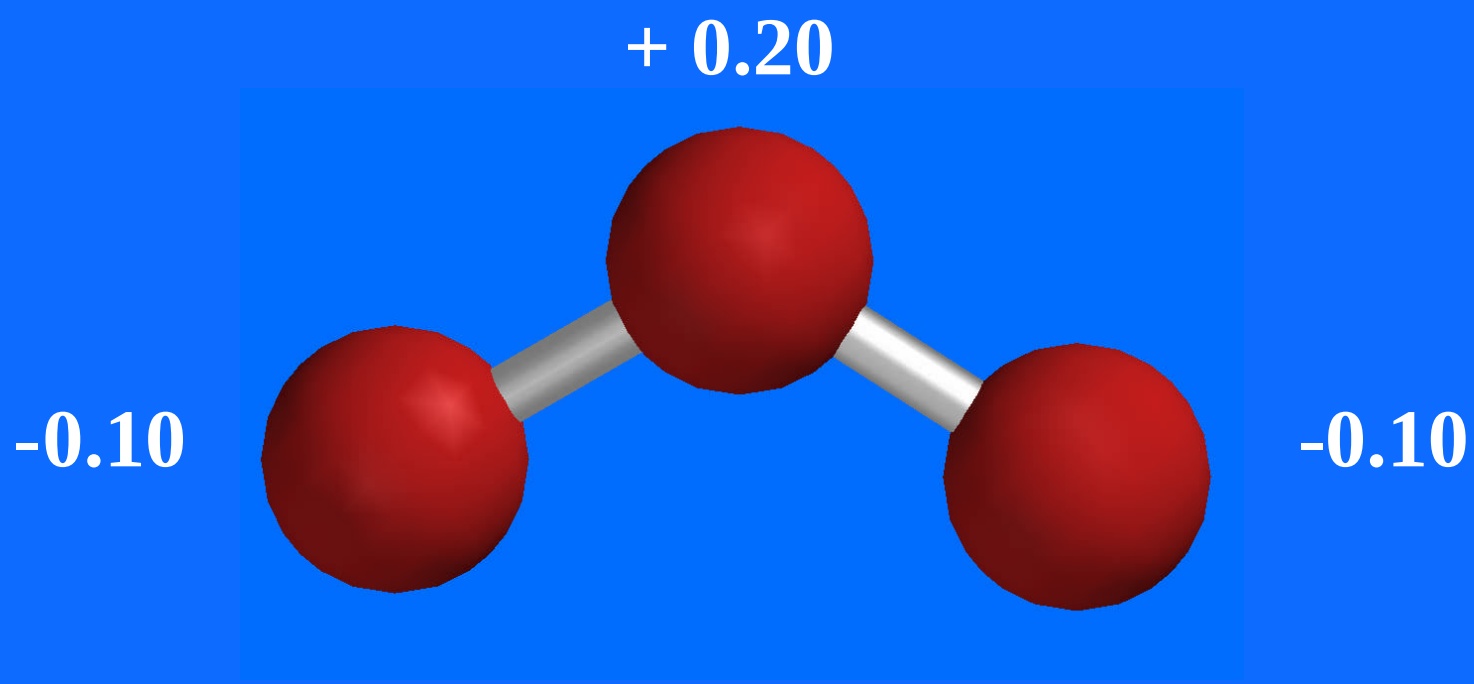




Resonance: A Familiar Concept

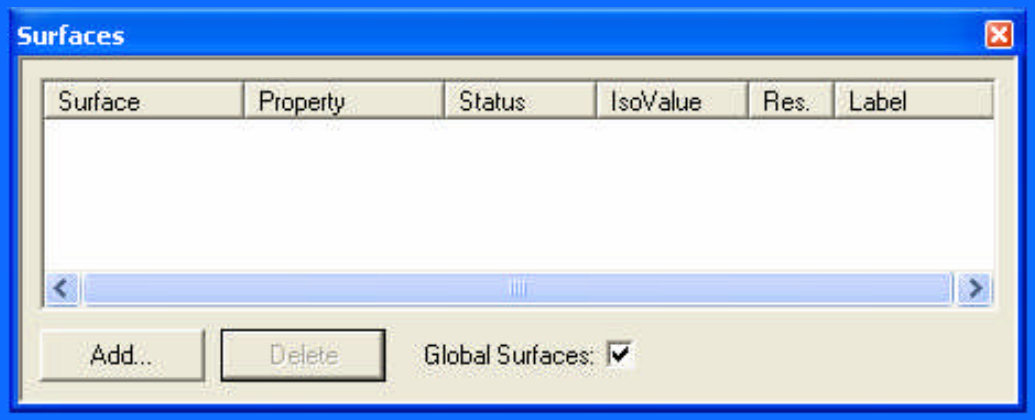
The symmetrical structure and HF/3-21G calculated charge distribution in ozone agree well with simple resonance models





Creating Surfaces

In either *Setup Surfaces* or *Display Surfaces*

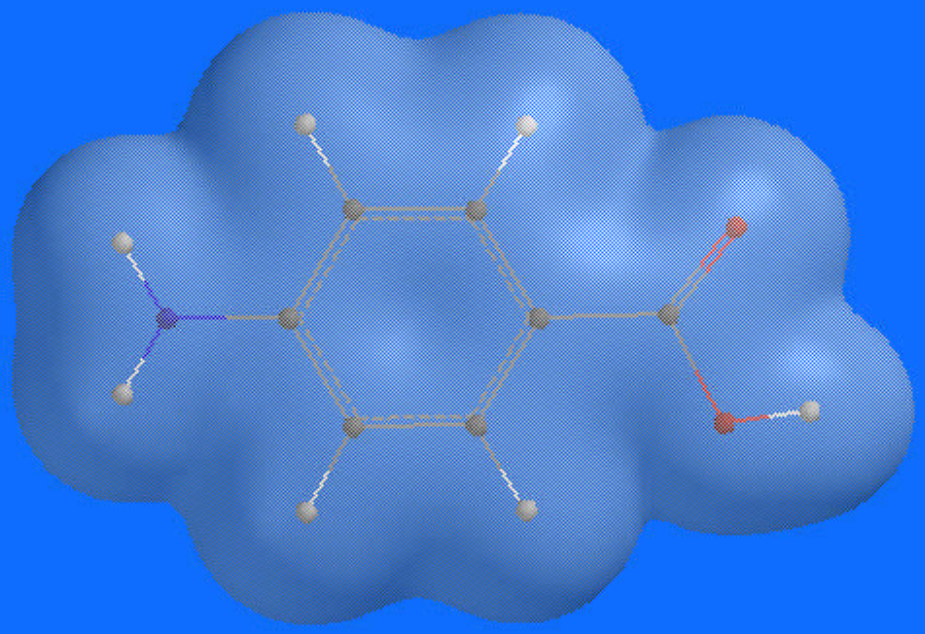


Add the following surfaces (using a low or medium resolution):

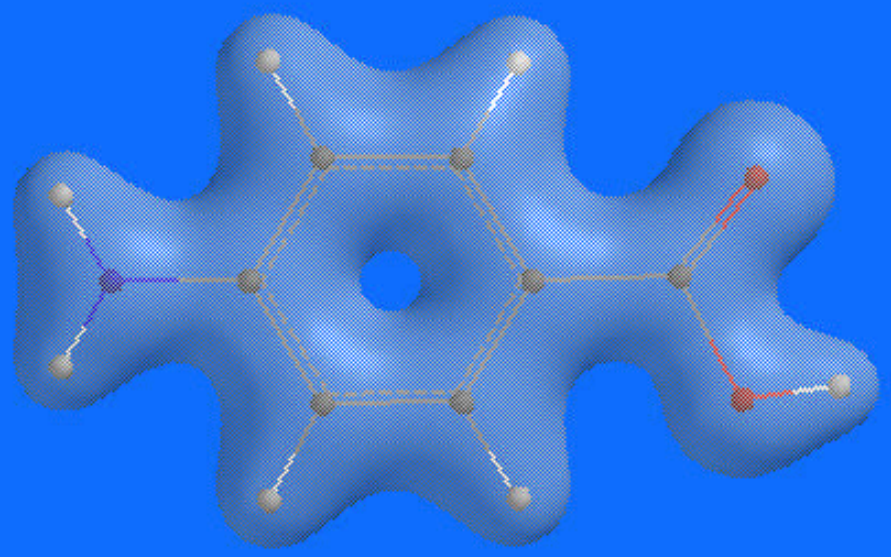
- Density
- Density (bond)
- Potential
- LUMO{+2}
- LUMO{+1}
- LUMO
- HOMO
- HOMO{-1}
- HOMO{-3} *(not a typo!)*

Resubmit the calculation.
(It only needs to do the surfaces!)

The Electron Density Surfaces of PABA

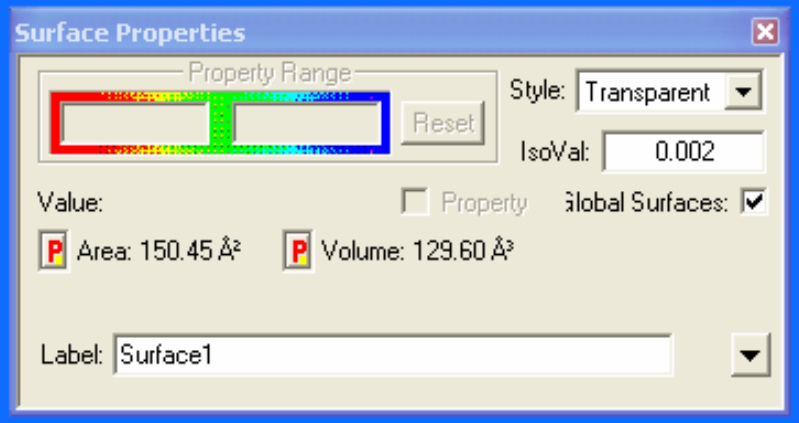


Density IsoVal = 0.002



“Bond” Density IsoVal = 0.08

The IsoVal setting in the Surface Properties box controls the “tightness” of the surface. Higher values of electron density give tighter surfaces.

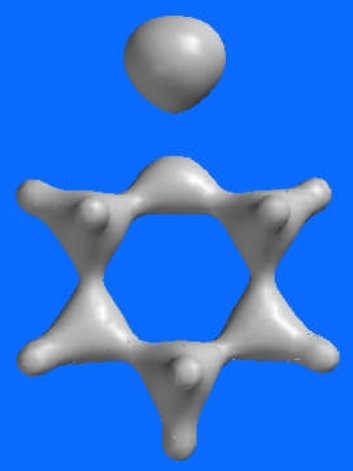


Electron Density Models

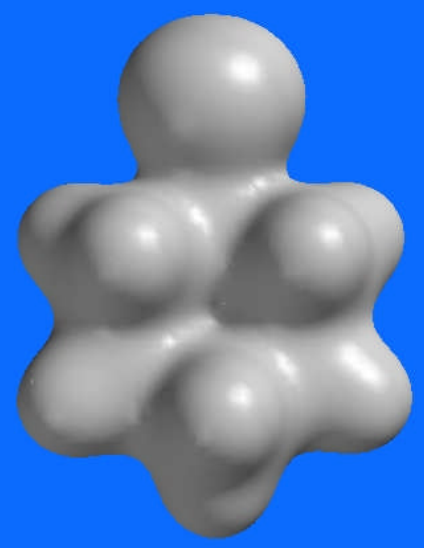
Electron Density models show the location of electrons

Large values of the density will first reveal atomic positions (the x-ray diffraction experiment) and then the chemical bonds, while even smaller values will indicate overall molecular size and shape

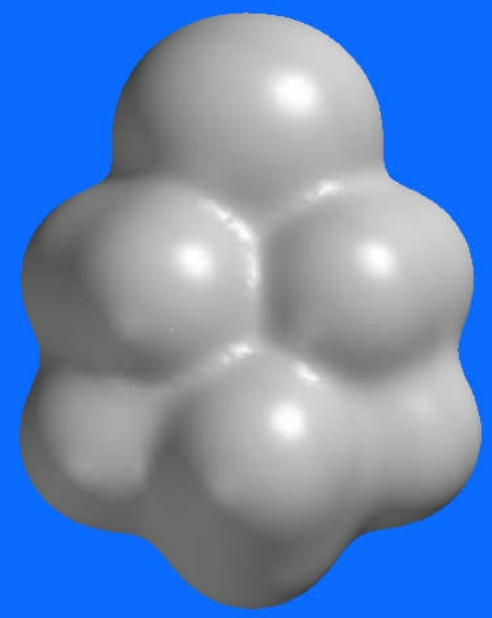
0.2 e^-/au^3



0.02 e^-/au^3

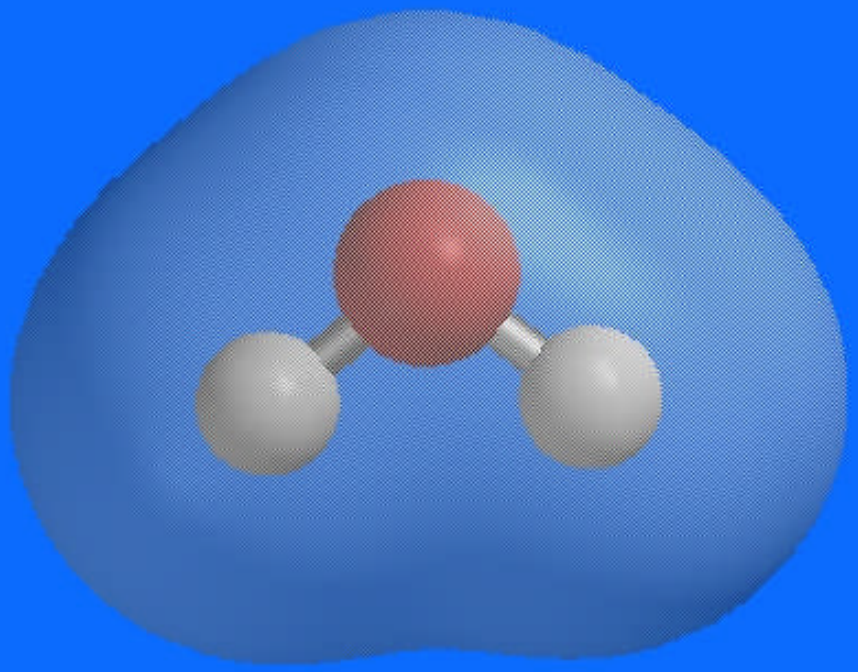


0.002 e^-/au^3



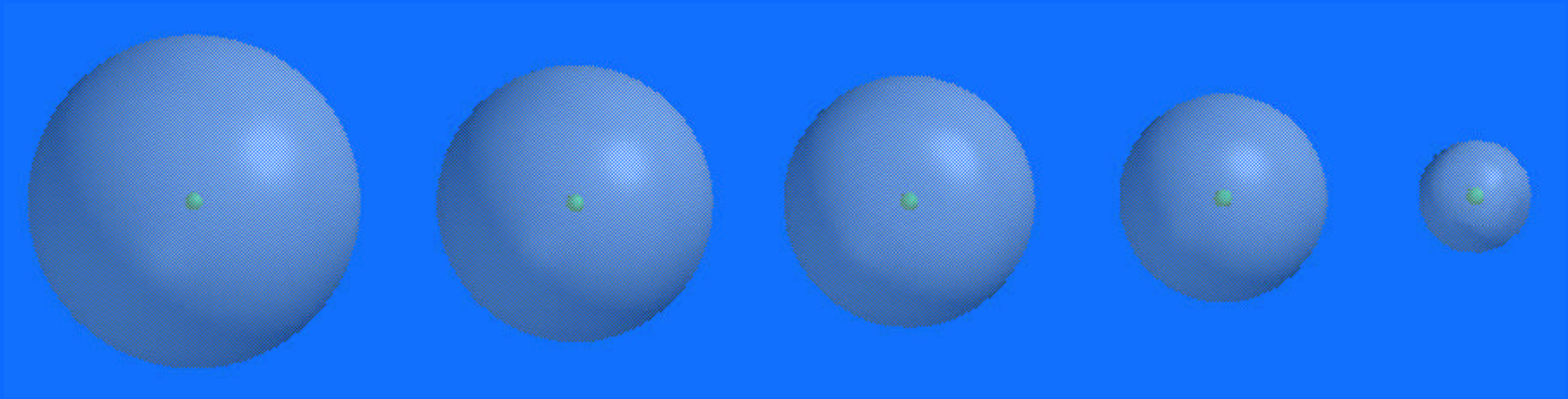
Size Density Surface

At a density of 0.002 e^-/au^3, the isosurface encloses >90% of the electron density of the molecule.



Size and Charge

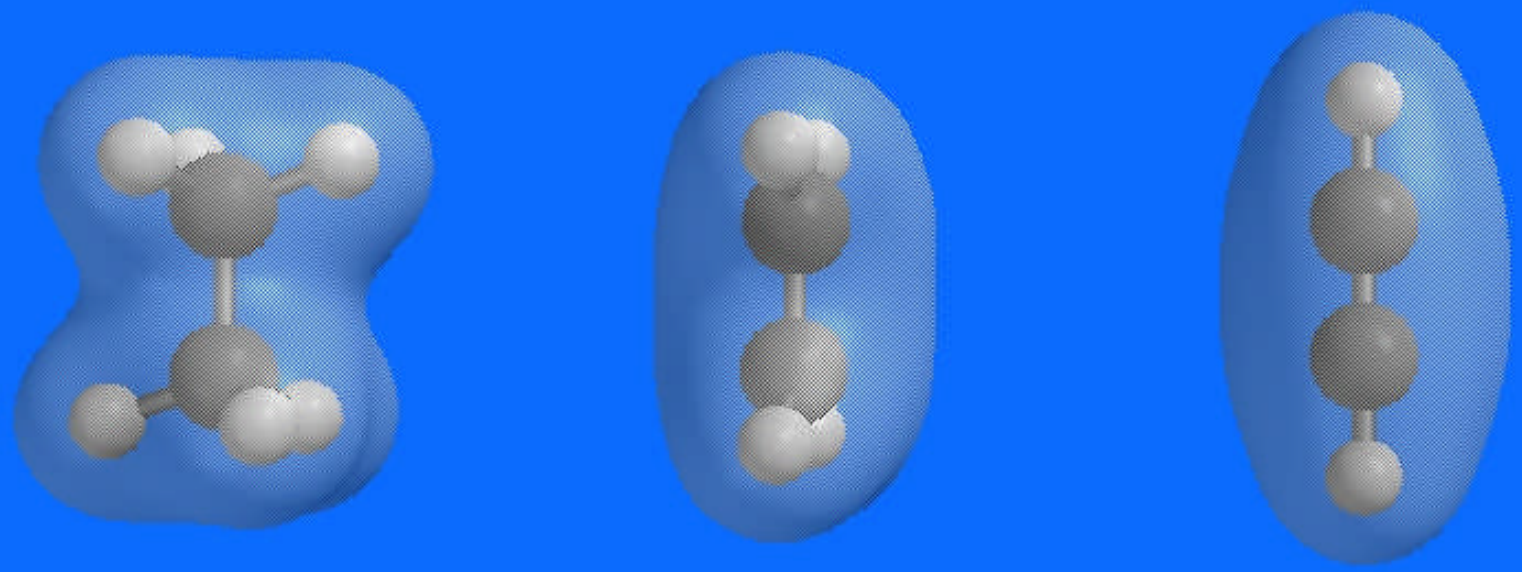
Size density surfaces of sulfur species



S^{2-} S^{0} S^{2+} S^{4+} S^{6+}

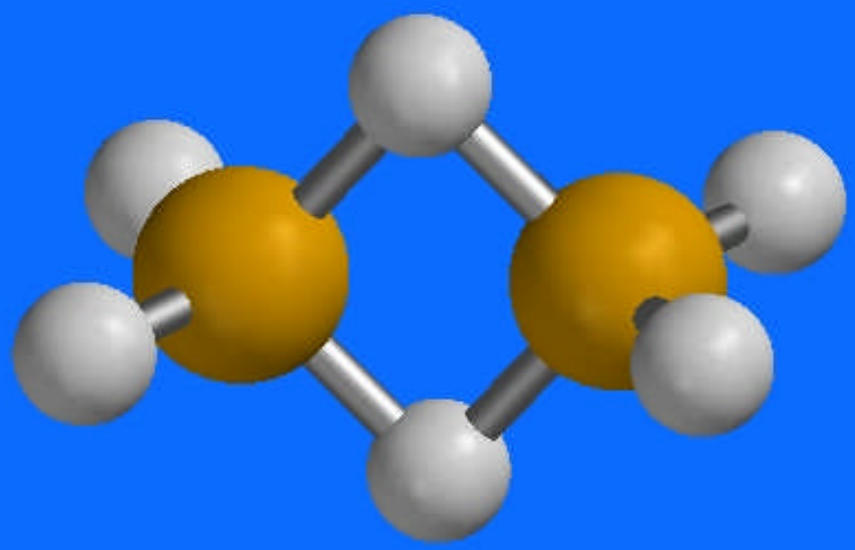
Electron Density Models

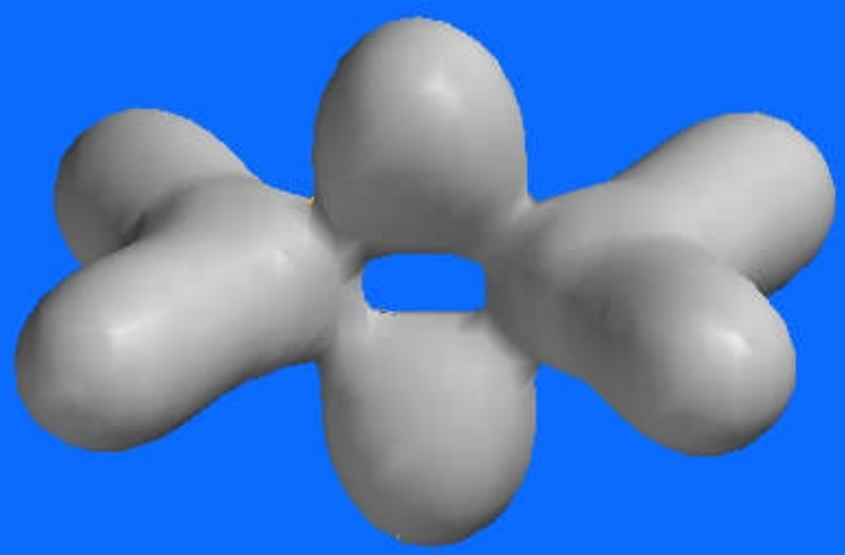
(Isodensity surface = 0.02 e^- / au^3)



To Bond or Not to Bond

Unlike conventional structure models that require bonds to be drawn explicitly, electron density models may be used to elucidate bonding. For example, the electron density model of diborane shows the absence of a boron-boron bond.



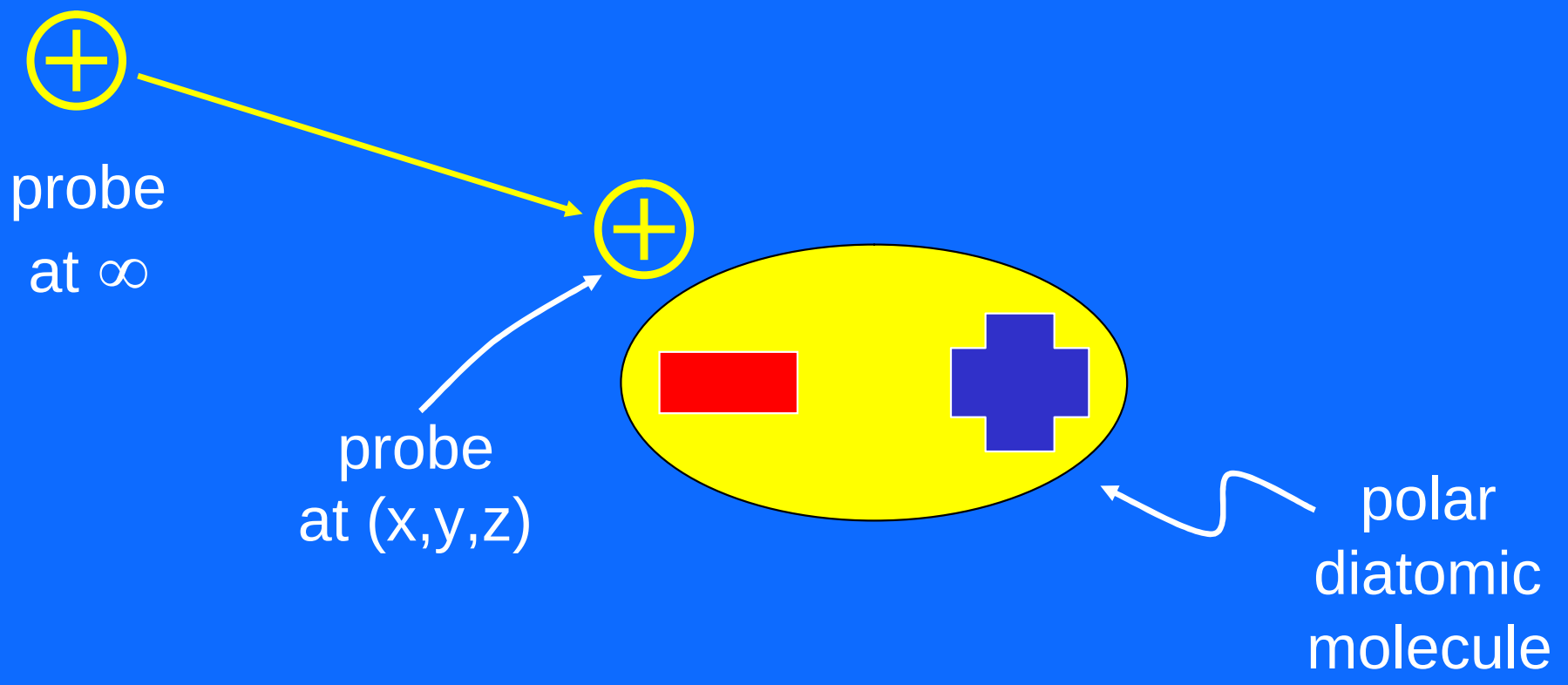


Density = 0.105 e^-/ au^3

Electrostatic Potential (ESP) Surfaces

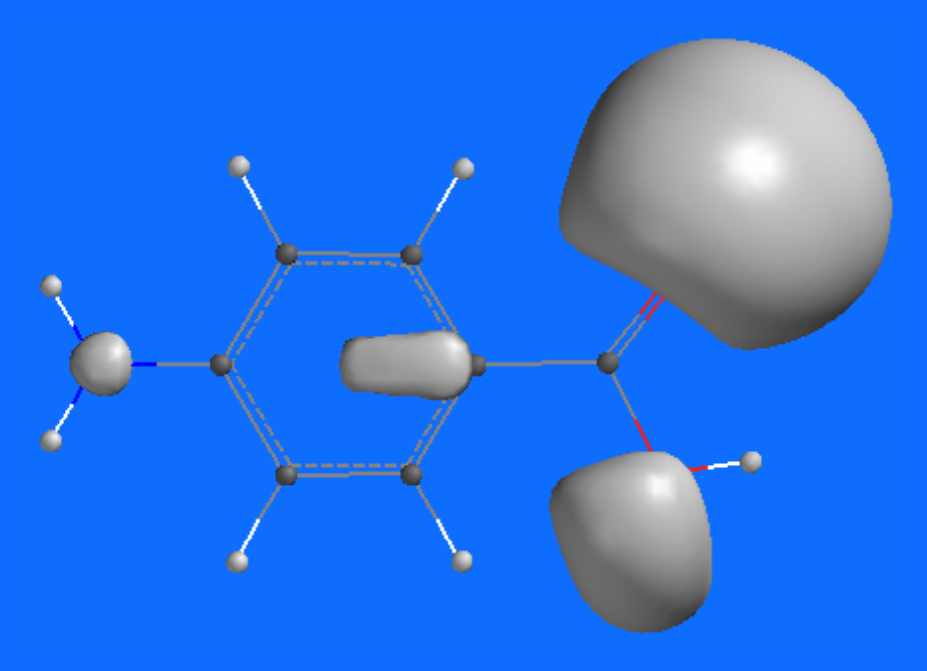
The electrostatic potential is the energy of interaction of a point positive charge with the nuclei and electrons of a molecule. Negative electrostatic potentials indicate areas that are prone to Lewis acids. Conversely, positive ESP's are areas prone to Lewis base attack.

What is Electrostatic Potential?

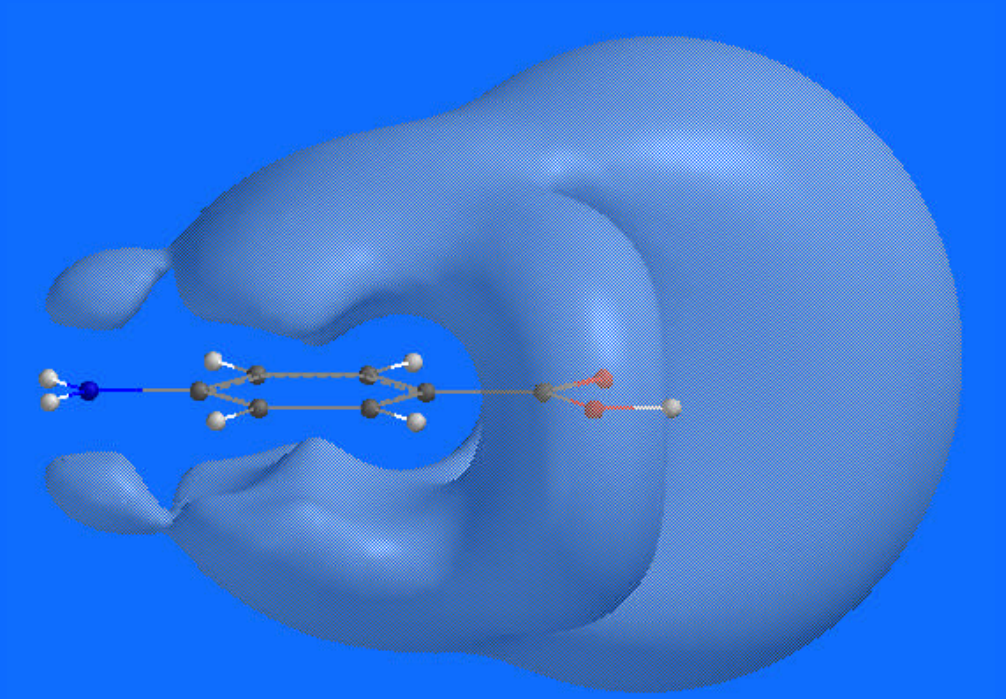


potential(x,y,z) = ΔE
when probe moves from infinity to (x,y,z)

The Electrostatic Potential Surface of PABA



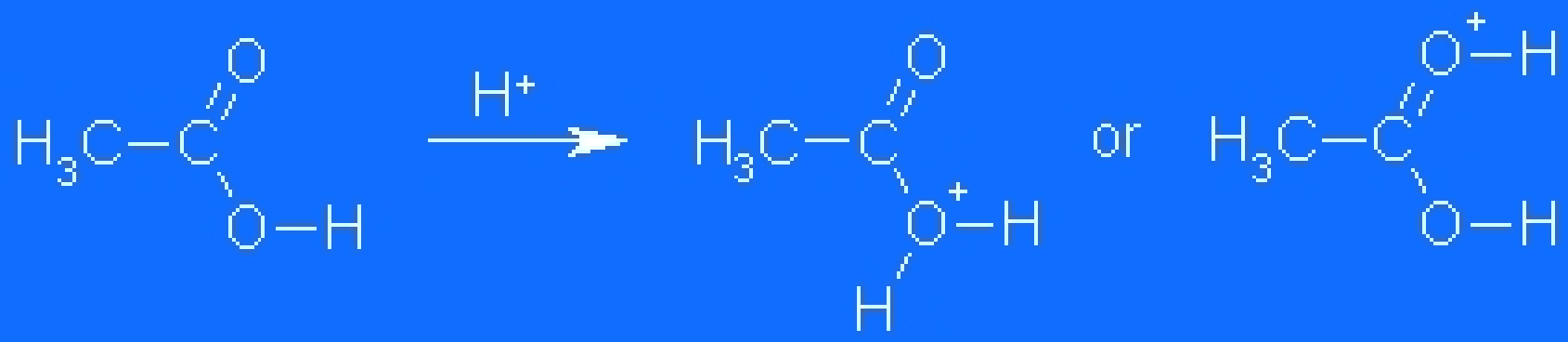
IsoVal = -20



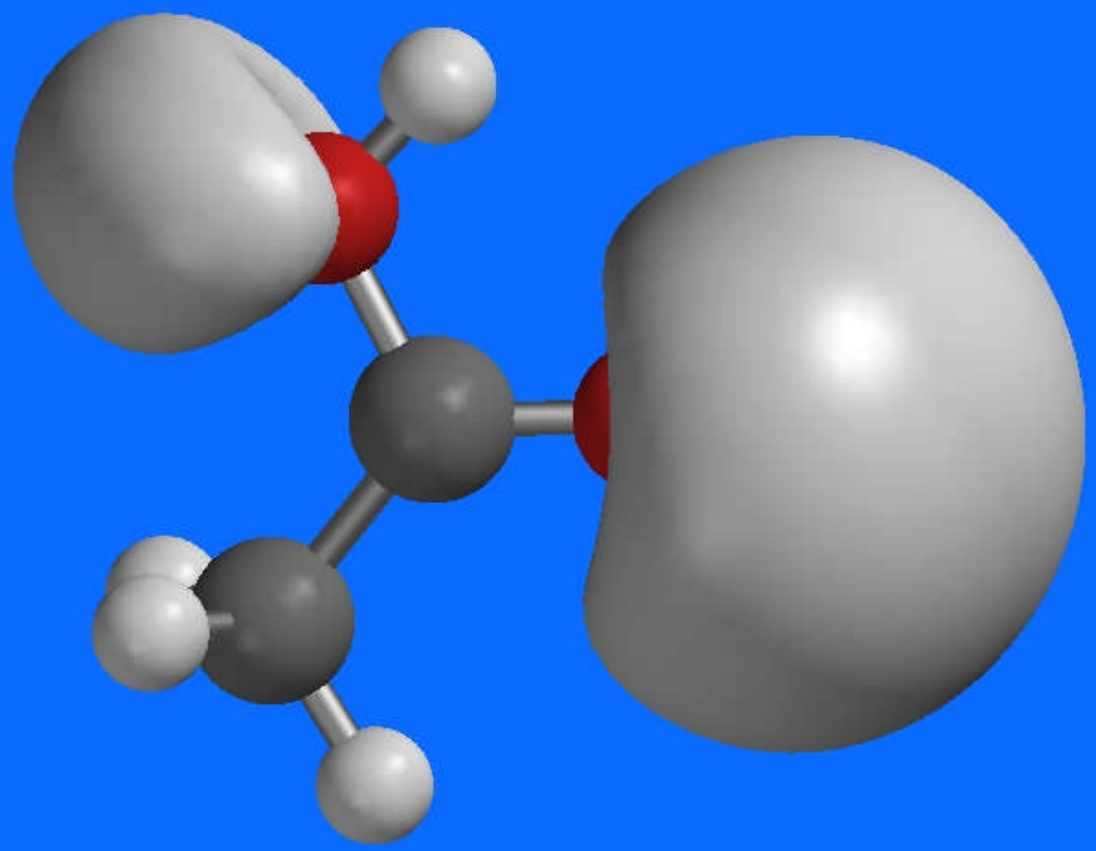
IsoVal = -6.6

Here again, the IsoVal setting in the Surface Properties box controls the “tightness” of the surface. Greater negative potential values give tighter surfaces.

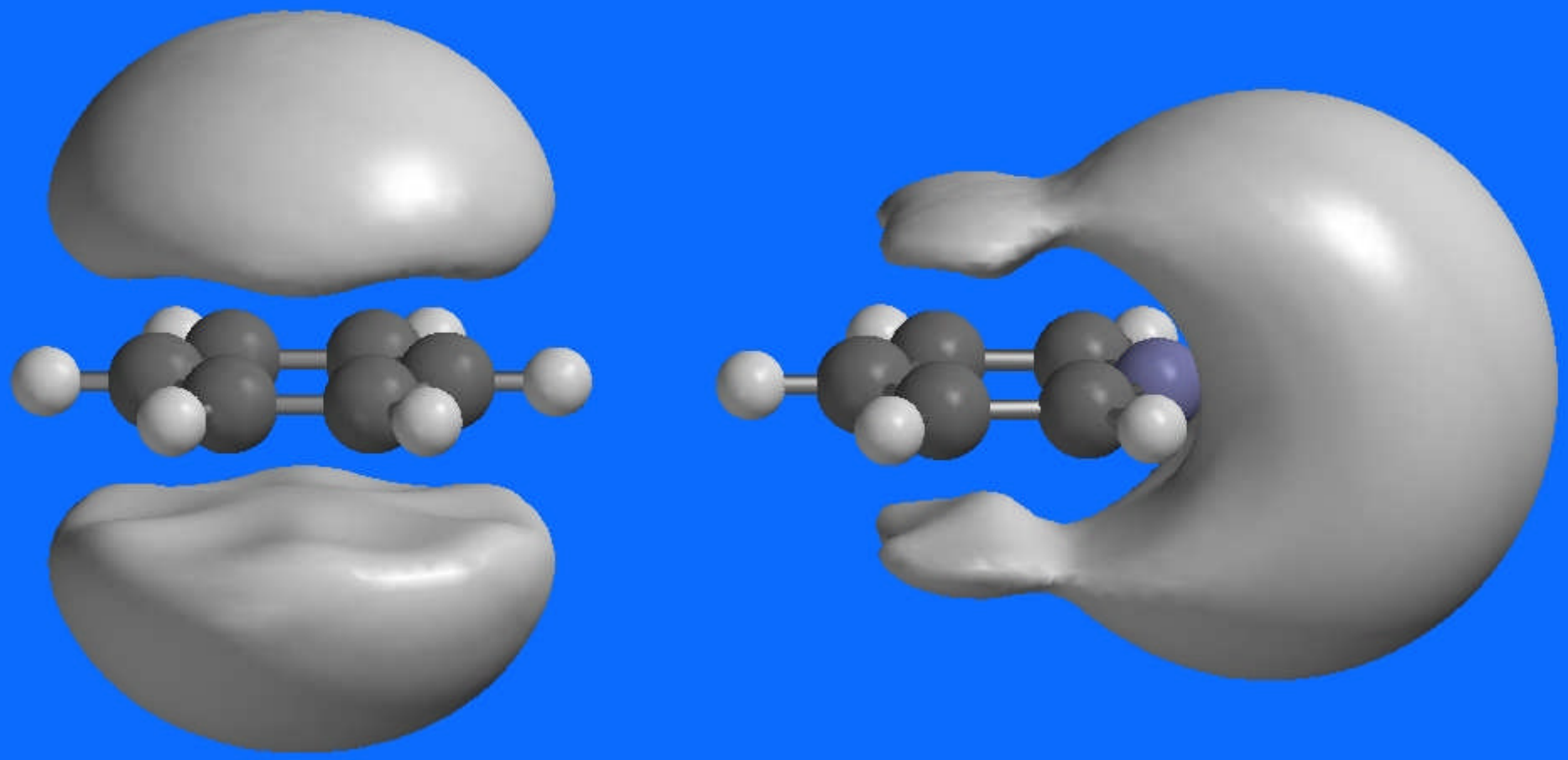
Protonation of Acetic Acid



Protonation occurs at the site of greater electrostatic potential. This is the first step in esterification.

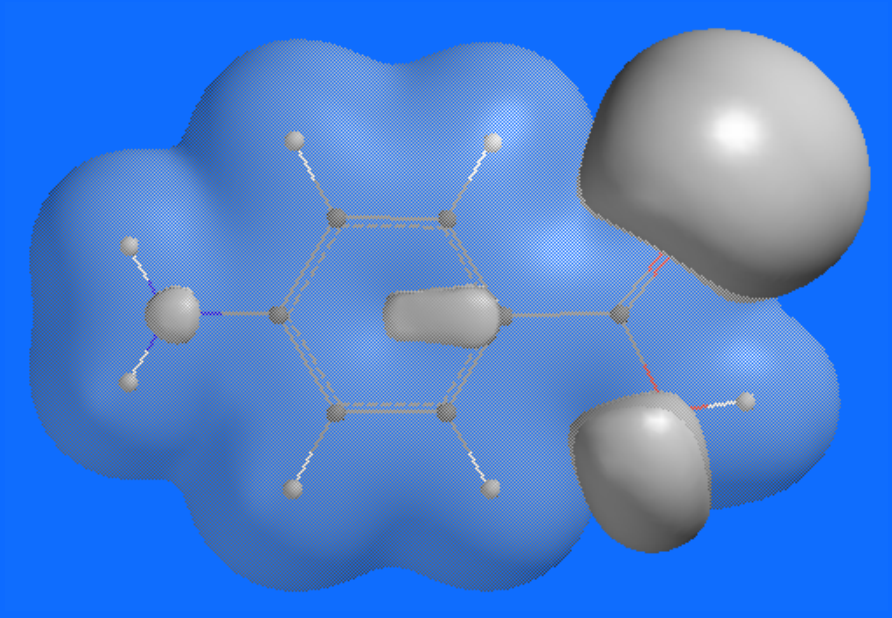


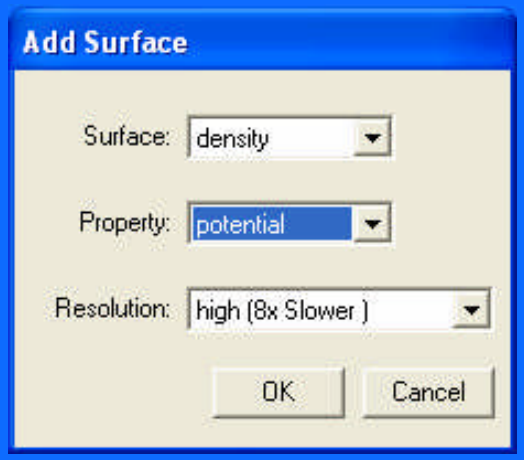
Electrostatic potential surfaces of benzene and pyridine



“Mapped” Surfaces

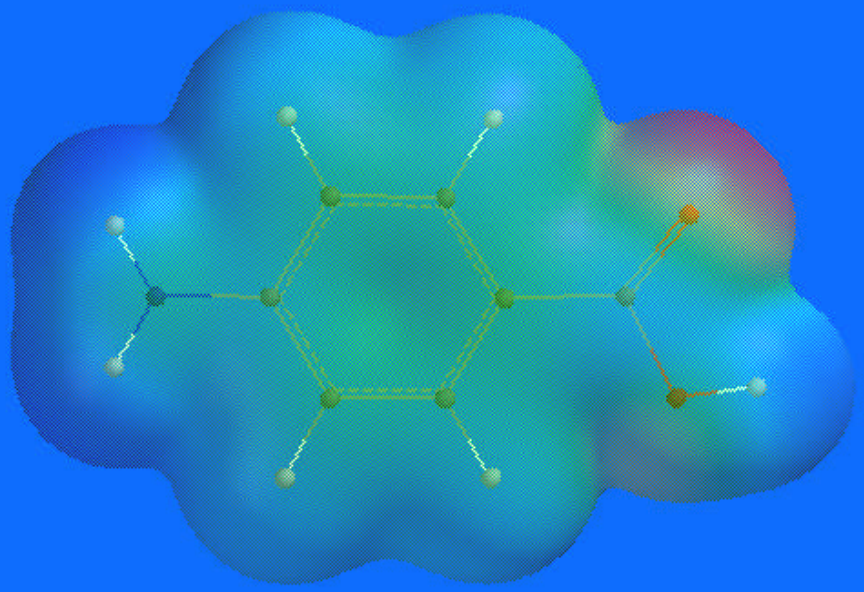
- Representing regions of Lewis acidity or basicity relative to a density surface can provide useful information about the regioselectivity of a molecule’s reactivity.
- Although the two surfaces can be shown simultaneously, the electrostatic potential can be *mapped* onto the electron density surface.
- Add a *Density* surface with a *Potential* property. (Note that since we have already calculated these surfaces individually, the mapped surface is automatically ready!)

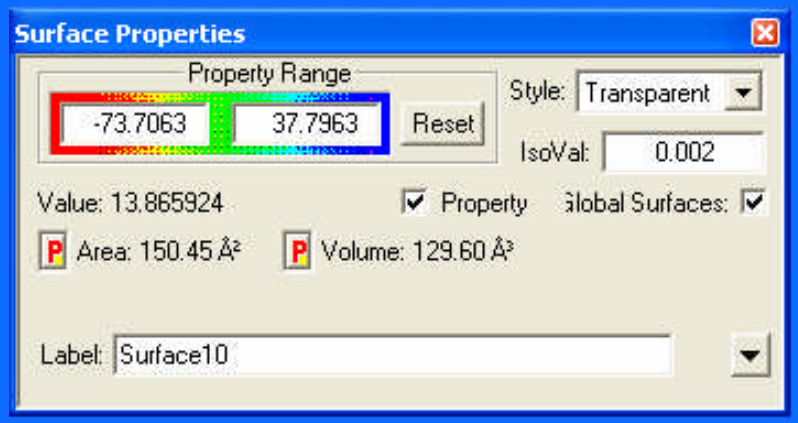




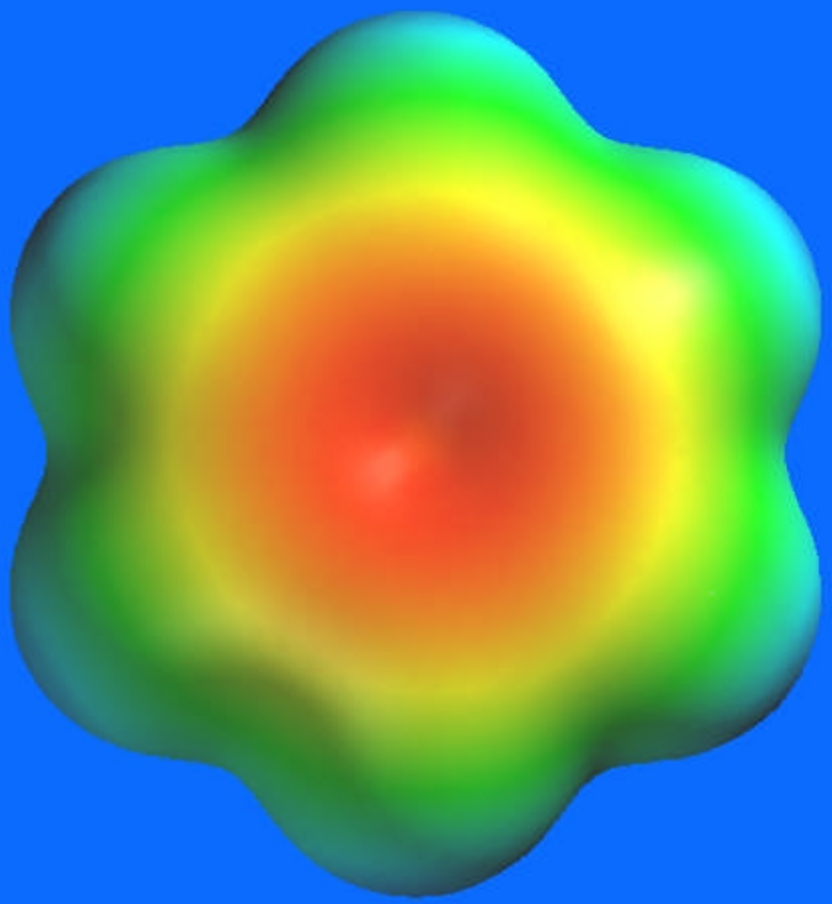
Electrostatic Potential Mapped onto the Electron Density Surface of PABA

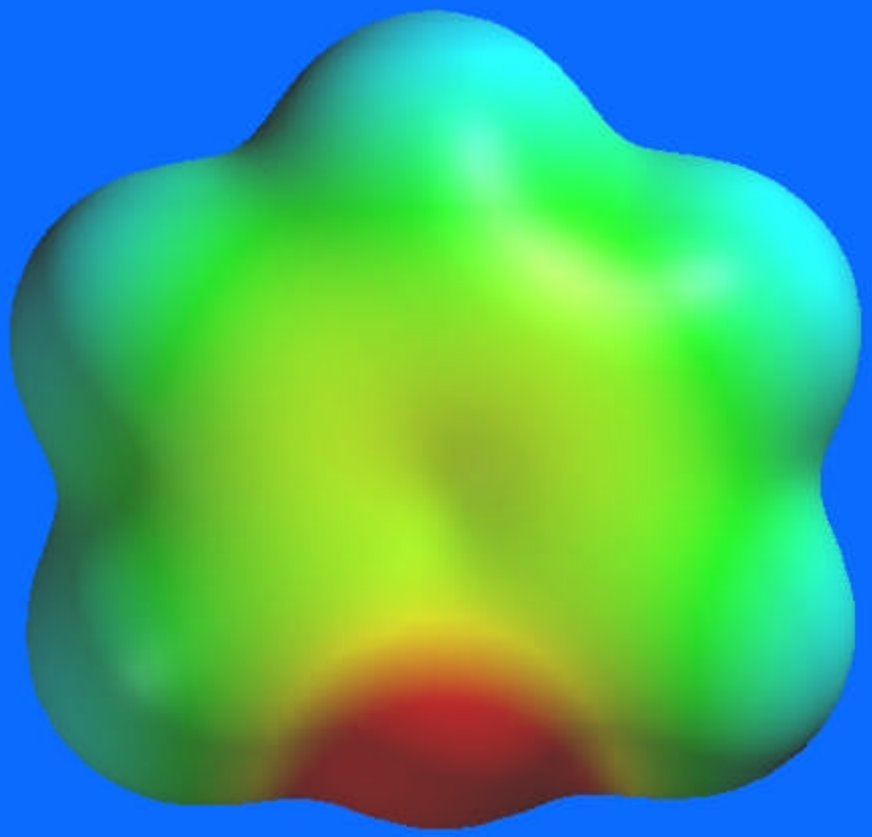
- This surface displays molecular size and shape (from the density map) and is colored to represent relative positive and negative regions of the surface.
- Colors toward red indicate negative values of the ESP, while colors toward blue represent positive potential values.
- The coloration range can be adjusted in the surface properties box.



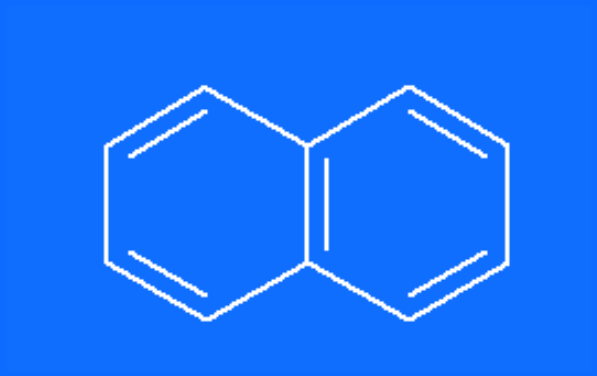


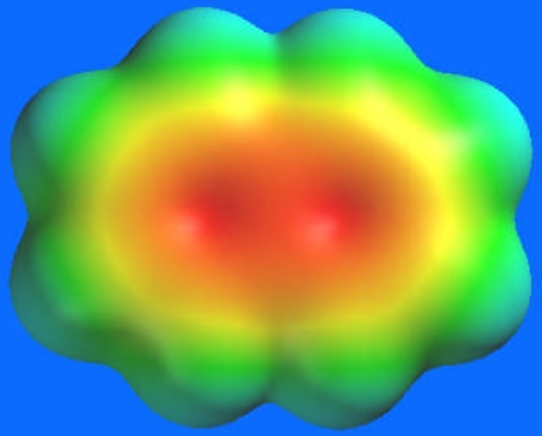
Benzene vs. Pyridine

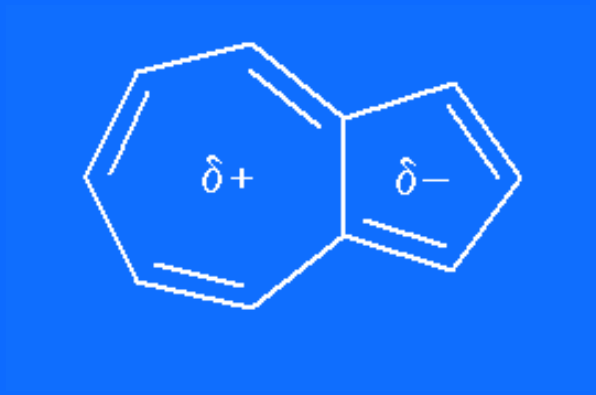


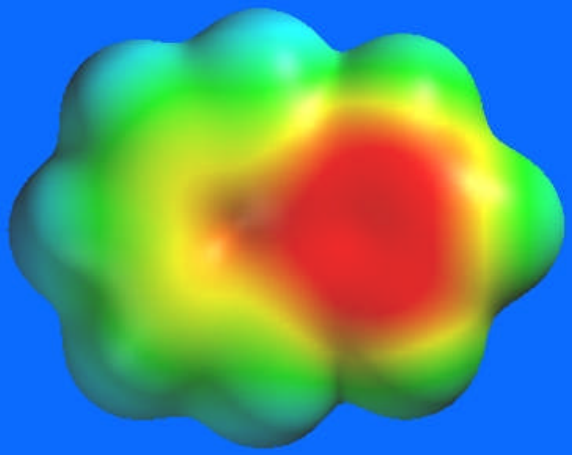


Naphthalene vs. Azulene



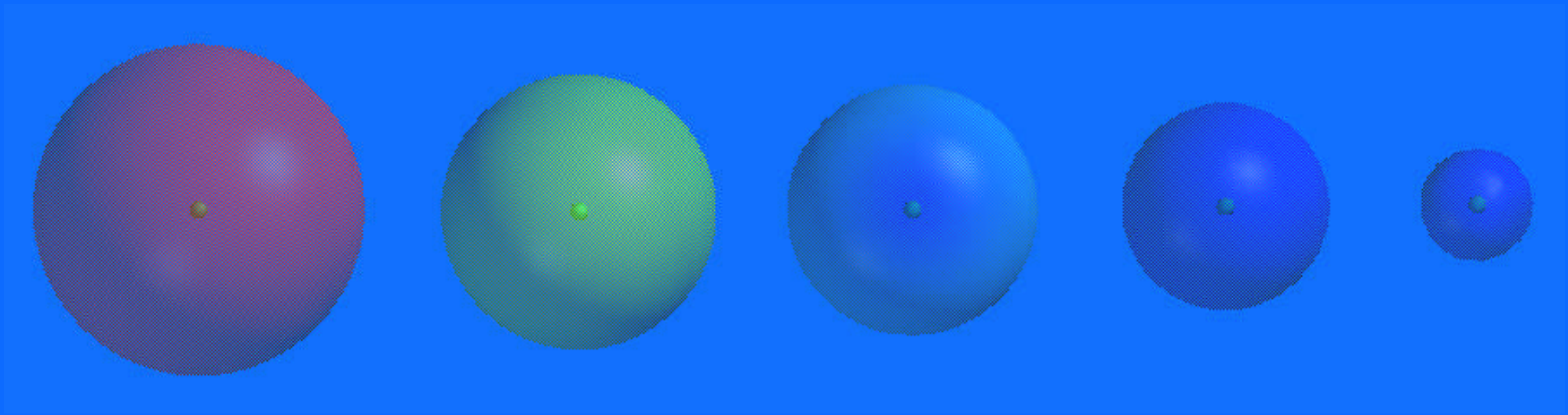






Remember these?

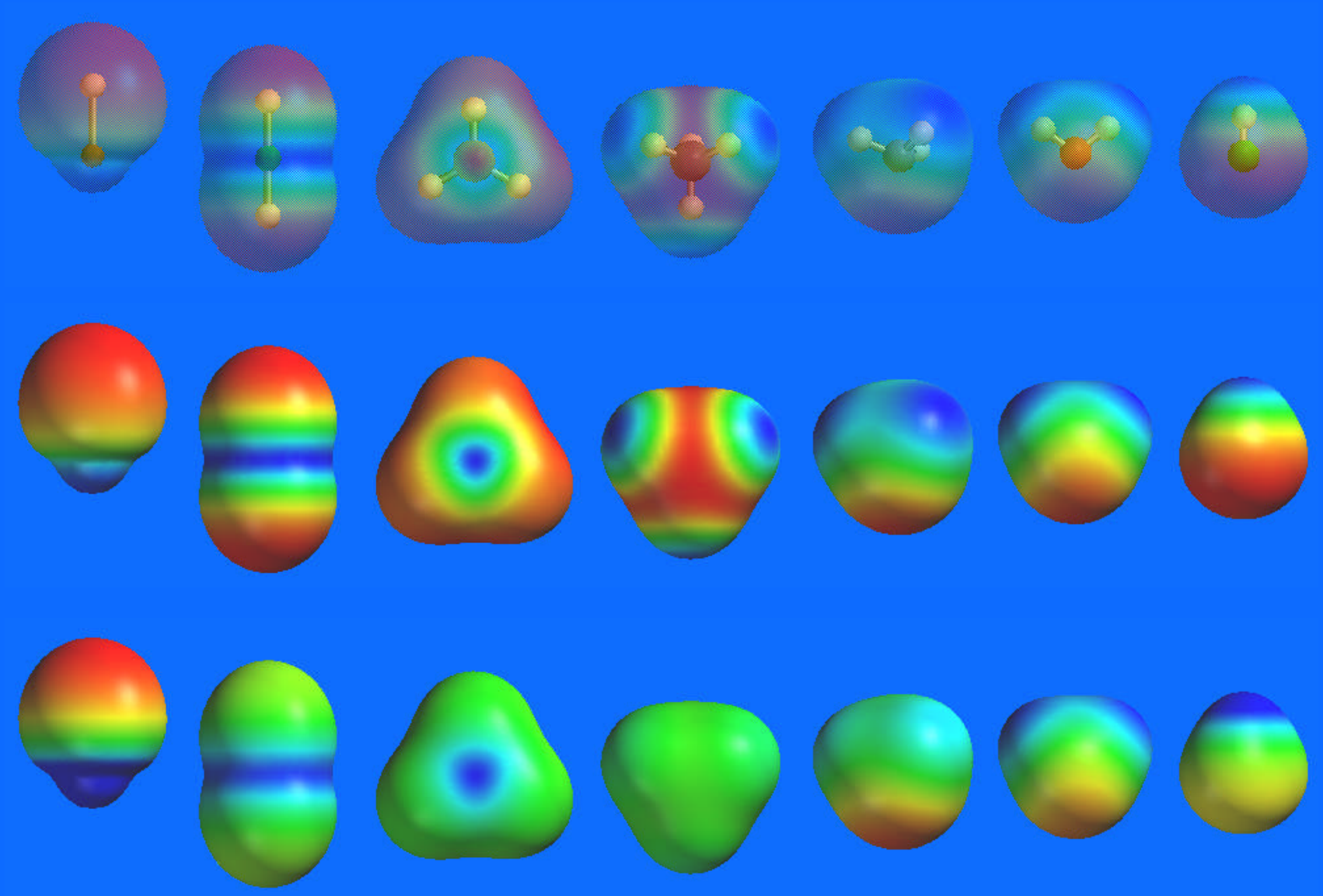
Size density surfaces of sulfur species



S^{2-} S^{0} S^{2+} S^{4+} S^{6+}

Easter Eggs?

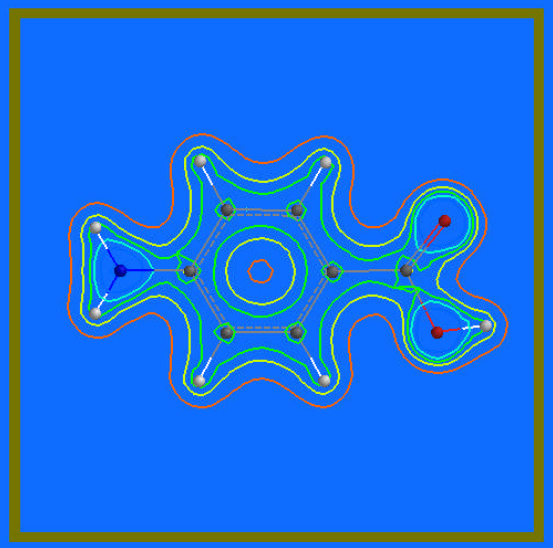
LiH BeH_2 BH_3 CH_4 NH_3 H_2O HF

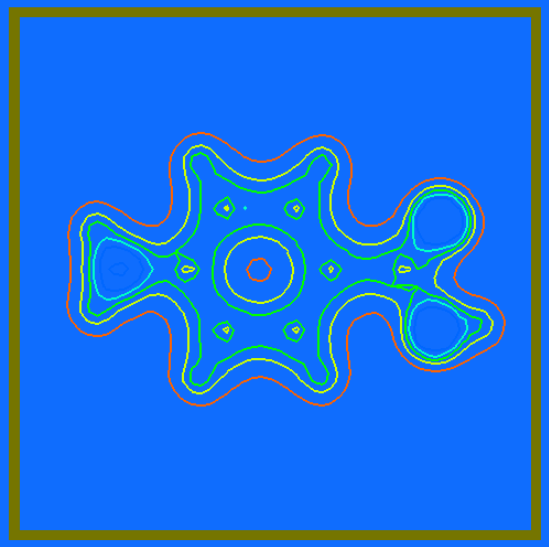


Slices

- The equivalent of taking a “CAT scan” through a surface
- To your PABA molecule, add a Slice Surface with a Density property, and a Slice Surface with a Potential Property. (Note that since we already have electron density information for PABA, the Slices are ready upon request!)
- Display each slice (one at a time). Click on the square and Shift/right-click dragging up to enlarge the frame.

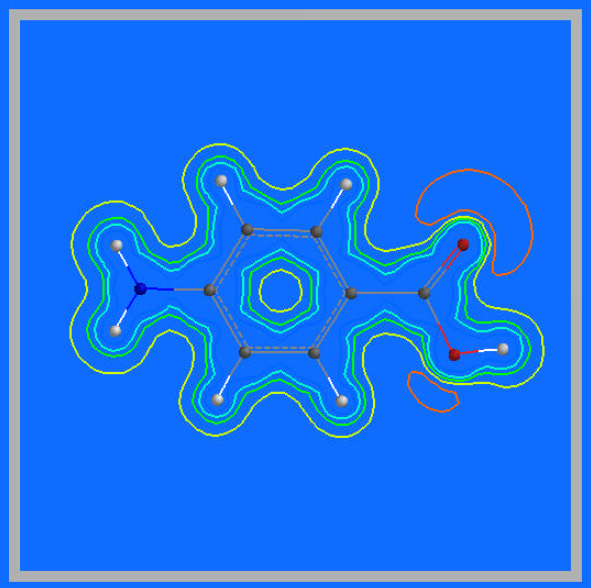
Electron Density Slice of PABA

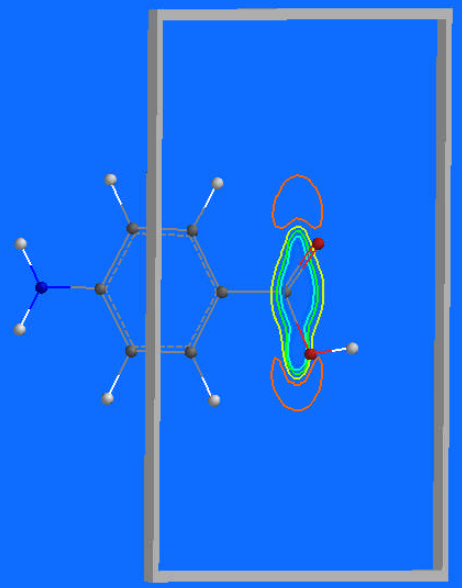




This type of slice is useful in discussions of X-ray crystallography (especially if the molecule is hidden).

Electrostatic Potential Slice of PABA

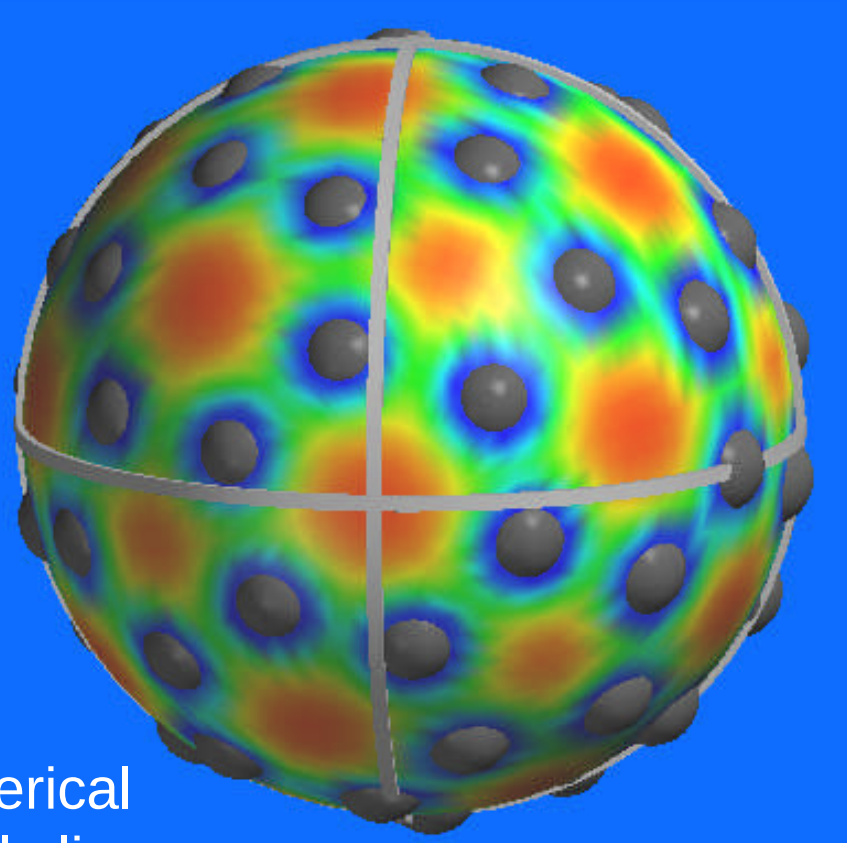




When selected, the slice plane can be rotated and translated relative to the molecule.

Other Displays for Slices

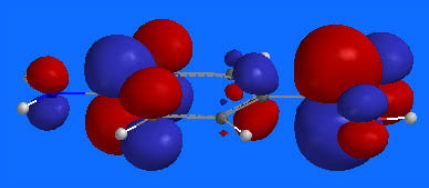
Slices can be displayed as contours, solid gradients, or transparent gradients, and can be planes, cylinders or spheres.



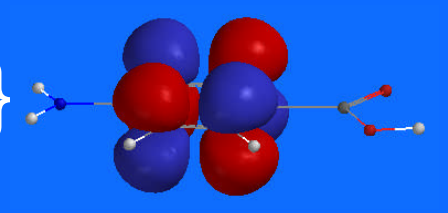
Buckyball with a spherical electrostatic potential slice

Molecular Orbitals of PABA

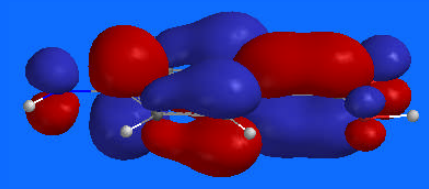
LUMO{+2}

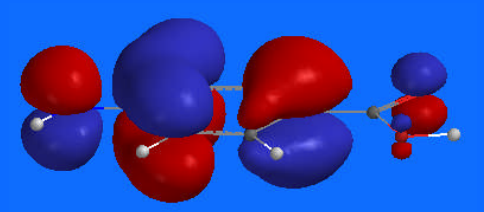


LUMO{+1}

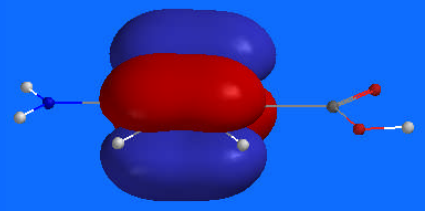


LUMO

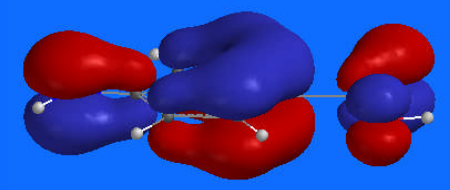




HOMO



HOMO{-1}

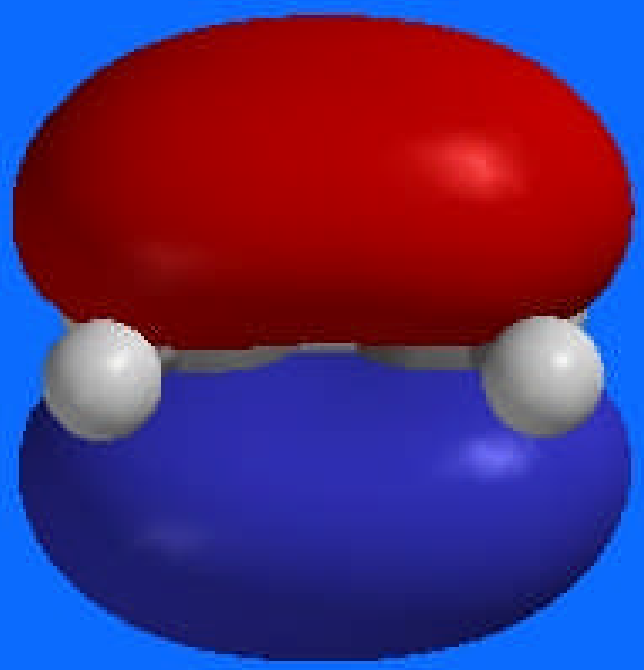


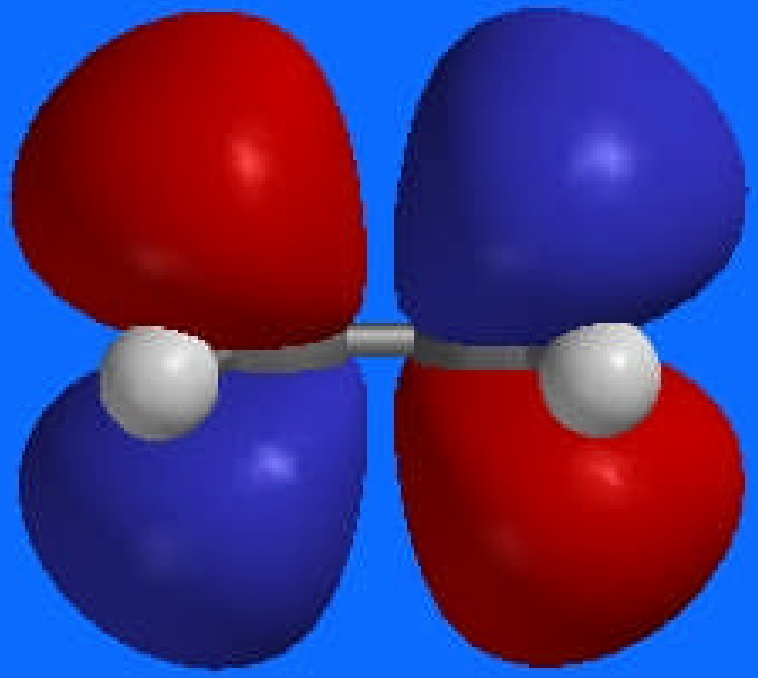
HOMO{-3}

Energy of the orbitals can be read in the Output text file

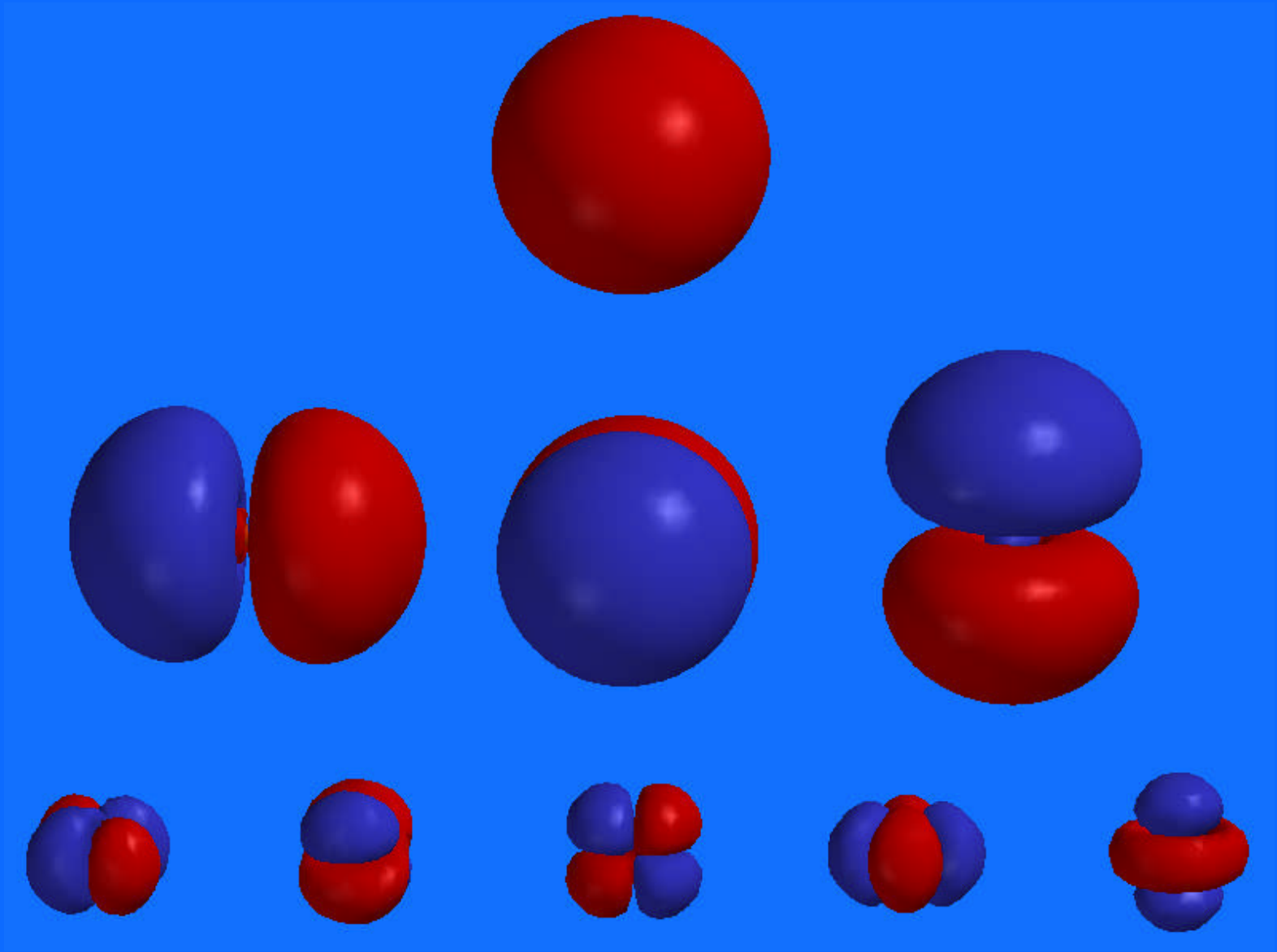
Molecular Orbitals of Ethylene

Visualizations and Tabulations

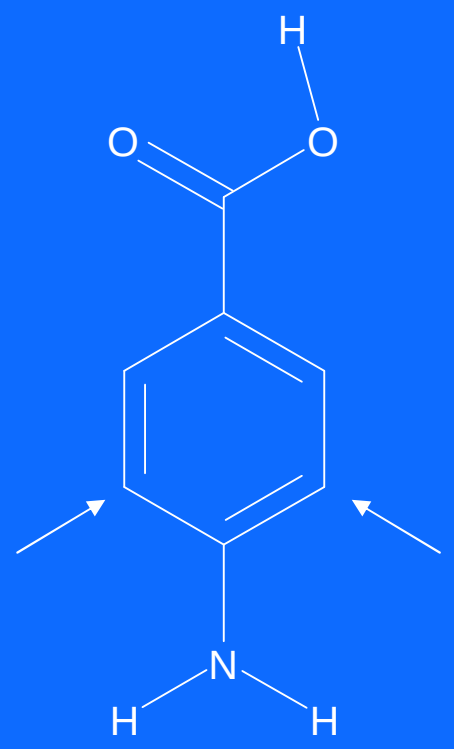


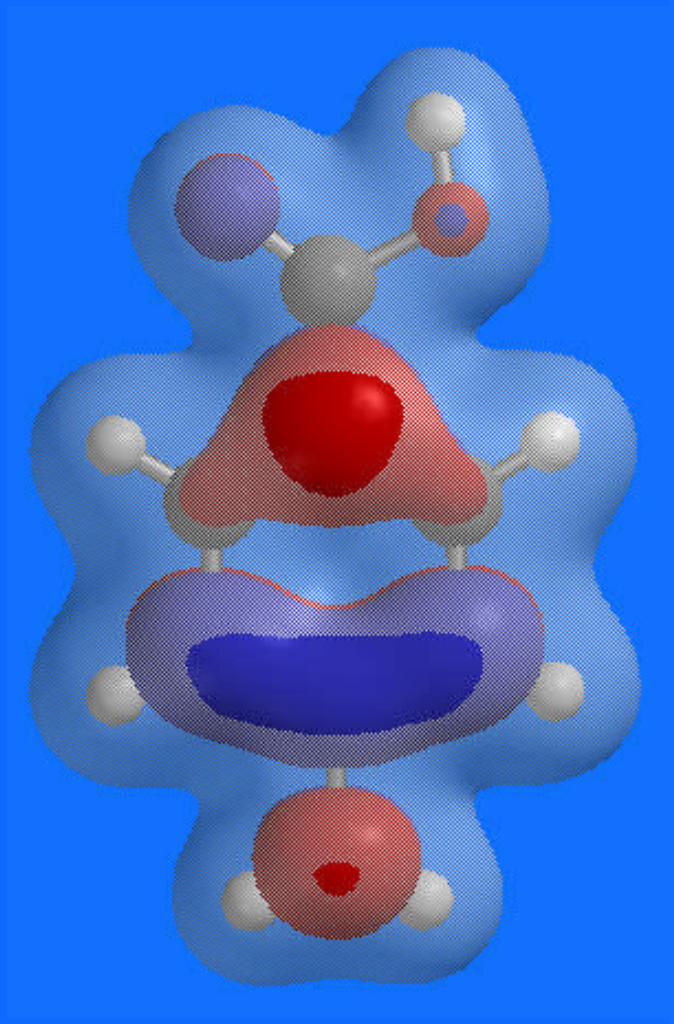


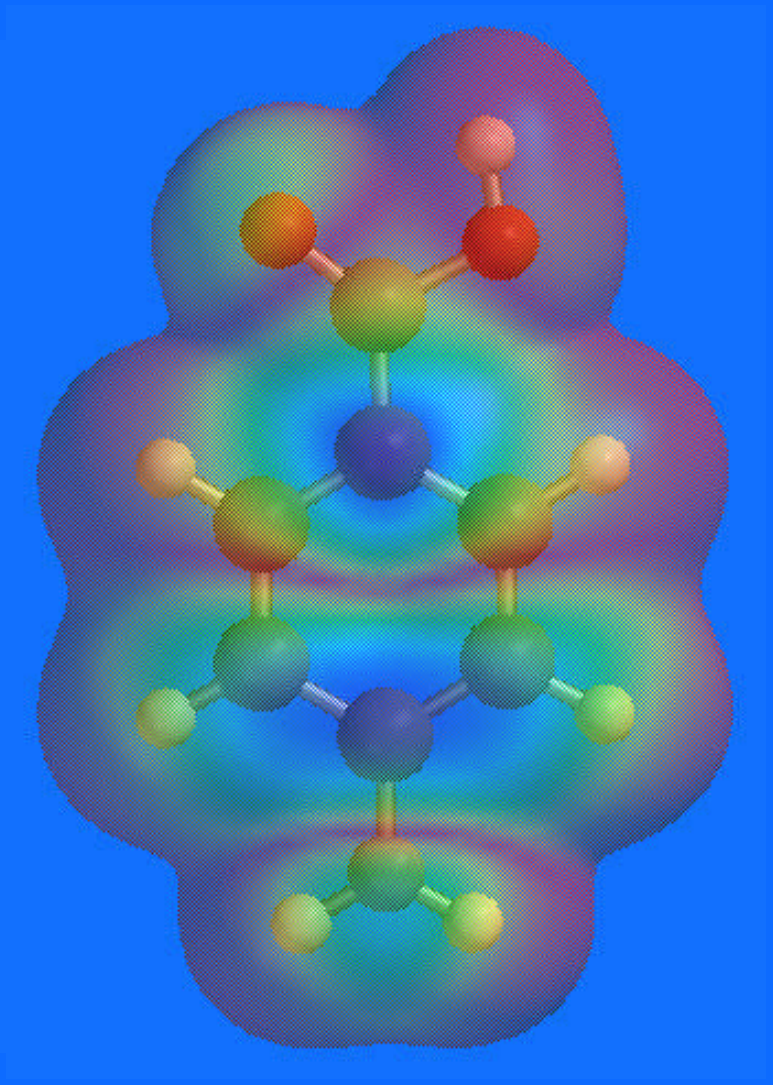
And of course… Atomic Orbitals



Mapping MOs onto the Density Surface – *Frontier Orbitals*





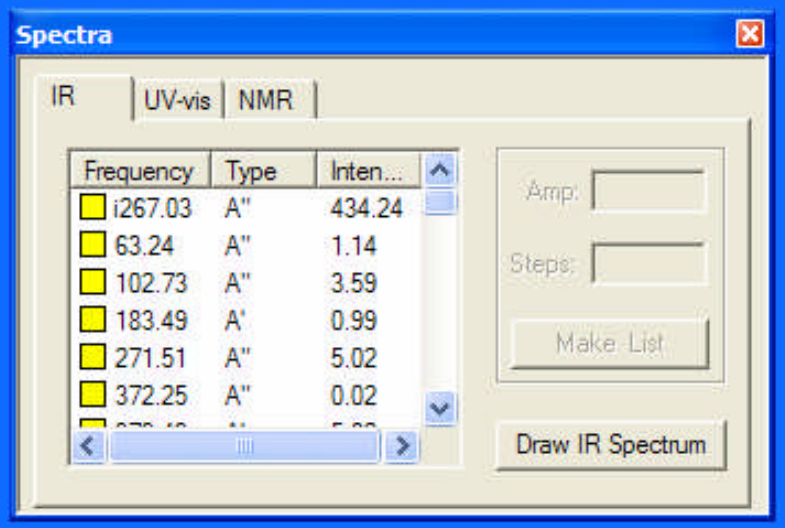


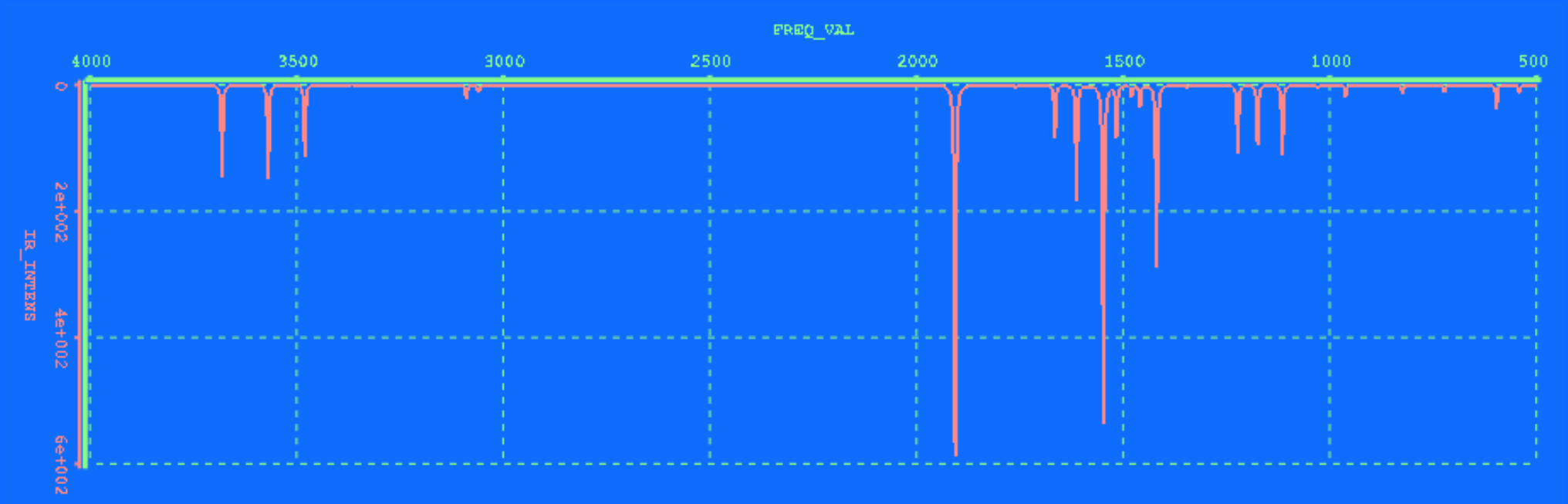
Where will electrophiles attack?

Density surface with HOMO property

Vibrational Modes of PABA

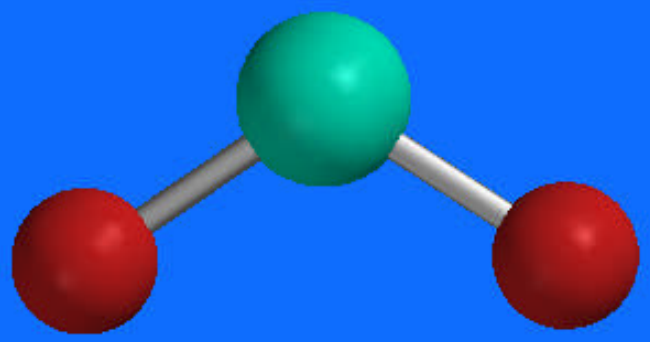
- Display Spectra, then IR
- Choose vibrations by wavenumber
- Adjust vibration using *Steps* and *Amplitude*
- View spectrum by *Draw IR Spectrum*





Vibrational Modes

Molecular vibrations for sulfur dioxide and other structures are easily animated to illustrate principles in physical chemistry, spectroscopy, and group theory. Looking “under the hood” into output files gives detail for advanced courses.

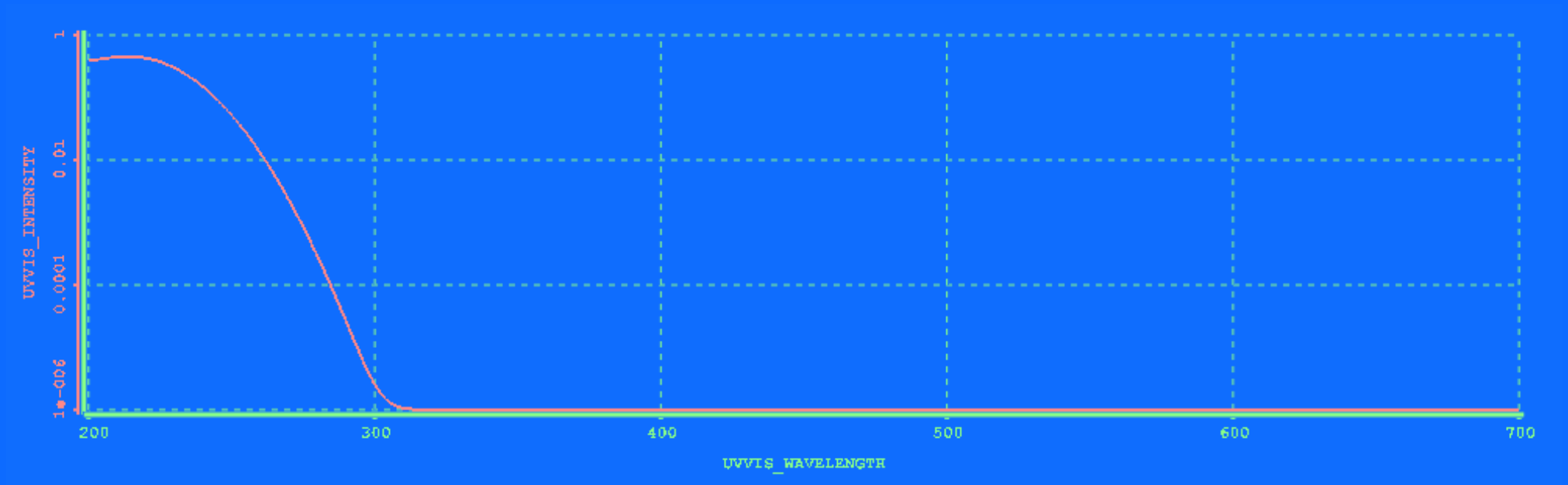


Normal Modes and Vibrational Frequencies (cm-1)

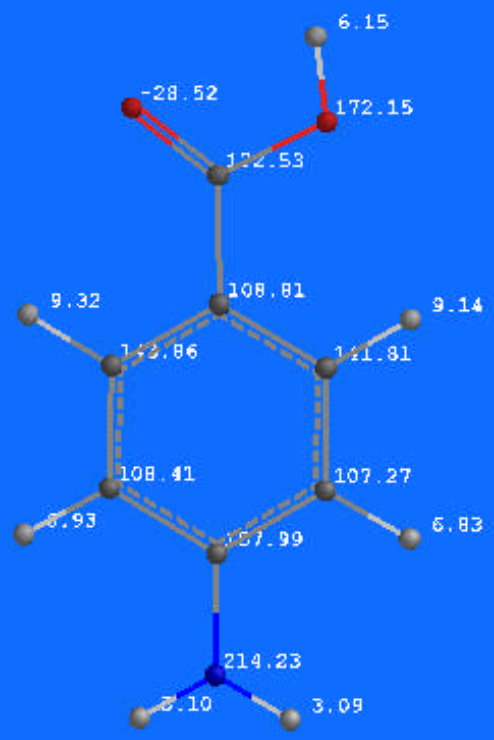
	601.54			1342.48			1575.26		
	A1			A1			B1		
	X	Y	Z	X	Y	Z	X	Y	Z
1	0.468	0.000	-0.375	0.530	0.000	0.331	0.461	0.000	0.273
2	0.000	0.000	0.530	0.000	0.000	-0.468	-0.652	0.000	0.000
3	-0.468	0.000	-0.375	-0.530	0.000	0.331	0.461	0.000	-0.273

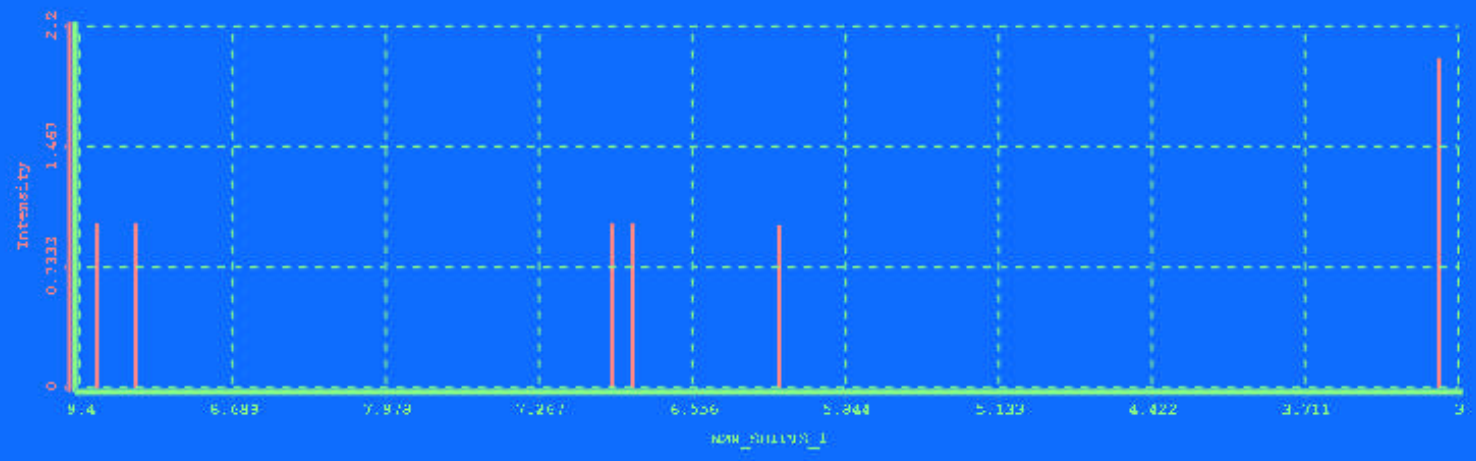
Zero-point vibrational energy: 5.031 kcal/mol

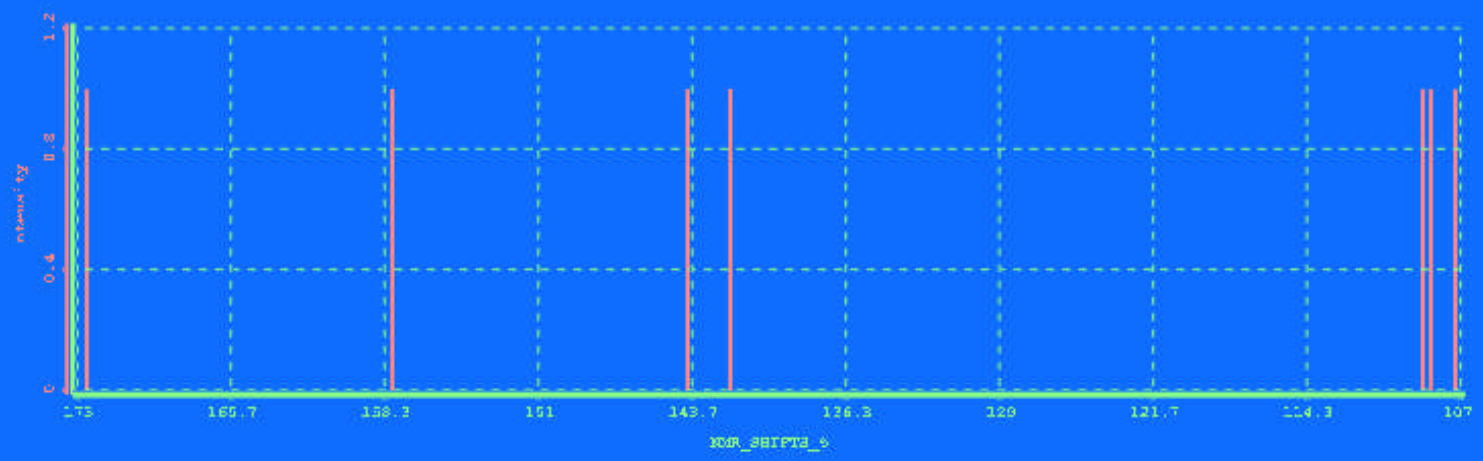
UV-Vis Spectrum of PABA



NMR Spectra of PABA







The “Natural” Structure of PABA?

Computation can predict the structure of PABA, but can we work with the structure as it is known to exist in nature?

Yes, with the Cambridge Crystallographic Data Centre (CCDC) database!

Searching the Cambridge Structure Database (CSD)

Wavefunction is now responsible for distribution of the Cambridge Structural Database (CSD) System (on Windows and Unix) to academic institutions in the United States.

The CSD currently contains more than 325,000 published X-ray crystal structures for organic and organometallic compounds. About 20,000 new structures are added annually. New versions of the CSD are released every six months. The CSD System includes the ConQuest search software used to interrogate all CSD information fields (bibliographic, chemical and crystallographic), and also includes IsoStar, a knowledge-base of intermolecular interactions. Other components of the distributed System are planned. Structure searching can also be done through Spartan ’02.

Now that we've become acquainted with Spartan, let's talk about versions

What's New in Spartan '04

- Plotting of IR spectra
- Theoretical Database –
  auto-named pre-calculated structures, some with IR data, open for additions
- User-constructed parallel database
- MDL ISIS/Draw input and output
- Smiles string input and output
- NMR – ability to predict chemical shifts
- Fast DFT for small molecules (≤200 basis sets)
- Solvation energies – QM/MM using polarized Amber 99
- Conformational searching under user-defined constraints (NOE Data)
- Generate and follow intrinsic reaction coordinates

Spartan ’04 Student Edition

- Similar to the full version of Spartan ’04, but with only Molecular Mechanics, Hartree-Fock and semi-empirical methods, and limited in molecule size.
- Also includes the new Spartan ’04 features of a theoretical database, plotting of IR spectra, and ISIS/Draw compatibility

Let’s take a look at

ODYSSEY

matter in motion

What is ODYSSEY matter in motion ?

A New Set of

Programs +
Associated Chemistry Content

for Teaching Concepts in

Introductory Chemistry

SPARTAN vs. ODYSSEY

matter in motion

Molecules / Small Clusters	↔	Bulk Matter
Energy Minimization (T = 0)	↔	Dynamics at Given Temperature
Organic / Inorganic / Medicinal / Biological	↔	Primarily General / Physical
Quantum Mechanics Engine	↔	Classical Molecular Dynamics SImulation Engine

Also: Integrated (DHTML) Chemistry Content

ODYSSEY matter in motion

Demonstrations → **Classroom Support**

ODYSSEY matter in motion

Activities → **Assignments (Worksheets)**

ODYSSEY matter in motion

Lab → **Laboratory**

ODYSSEY
matter in motion

…is interactive:

- Stop-’N-Go Dynamics
- Sample Manipulation
- Property Queries
- Plotting

…**all** “on-the-fly”, initiated and controlled by the *student*

ODYSSEY
matter in motion

…is self-contained:

- Fully integrated chemistry content
- Only “print component”: ***Activity*** Worksheets (printed out and turned in by students)
- *Fully electronic version will be available later*

ODYSSEY
matter in motion

…is structured:

- Scripted DHTML links take students from step to step while completing worksheets

ODYSSEY
matter in motion

…is open-ended:

1) From the ***student***'*s* perspective:

Activities — open-ended analysis
if desired

Lab — completely open-ended
if desired

ODYSSEY
matter in motion

…is open-ended:

2) From the ***instructor's*** perspective:

"Open source" chemistry content:

— DHTML-formatted content included with the program

— Instructors can customize and add to the content base *if desired*

Customization:

…annotate pages

…change sample(s)

…change text [1]

…even create your own page ! [1]

---

[1] With standard HTML editor
[such as Microsoft FrontPage]

ODYSSEY
matter in motion

Demonstrations / Activities

…scripted and yet open-ended !

System Requirements

- Windows XP
- IE 6

- 1 GHz CPU
- 256 MB RAM
- 1 GB Disk

- Internet Access for Registration

ODYSSEY matter in motion

…in the Introductory/General Chemistry Curriculum:

⋮

- Thermochemistry
- **Gases**
- **Liquids/Solids/Intermolecular Forces**
- **Solutions**
- Kinetics
- Chemical Thermodynamics

⋮

Let’s take a look at

ODYSSEY

matter in motion

ODYSSEY
matter in motion

"Packaged" Chemistry Content

Activities

(Initial Release)

→

~60 Worksheets
of 3-5 Questions Each

Demonstrations

(Initial Release)

→

~70 Topics

Products

Student Edition

ODYSSEY matter in motion

Activities

Instructor's Edition

ODYSSEY matter in motion

Demonstrations

ODYSSEY matter in motion

Activities,
with Answer Key

Laboratory Edition

ODYSSEY matter in motion

Lab

ODYSSEY matter in motion

Demonstrations

Release Schedule

ODYSSEY matter in motion

Student Edition

(Windows)

ODYSSEY matter in motion

Instructor's Edition

(Windows)

Late Summer / Fall 2003

ODYSSEY matter in motion

Laboratory Edition

(Windows)

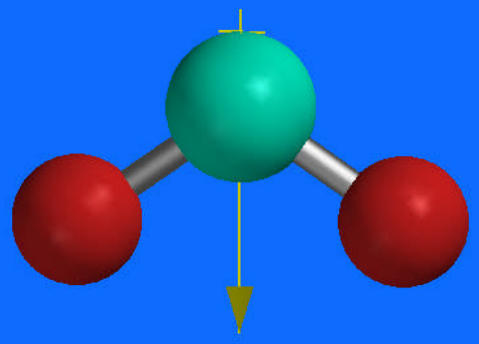
Early 2004

Let’s get back to Spartan

Animations

IR-Active Vibrational Modes and the Change in Dipole

- Close PABA, and create a SO_2 molecule
- Calculate an Equilibrium Geometry using HF 6-31G*, computing Frequencies
- Display Frequencies
- Select the IR-active B_1 mode
- Make List
- Close the original molecule (the one that is still vibrating)



Now let’s get information from this “list molecule”

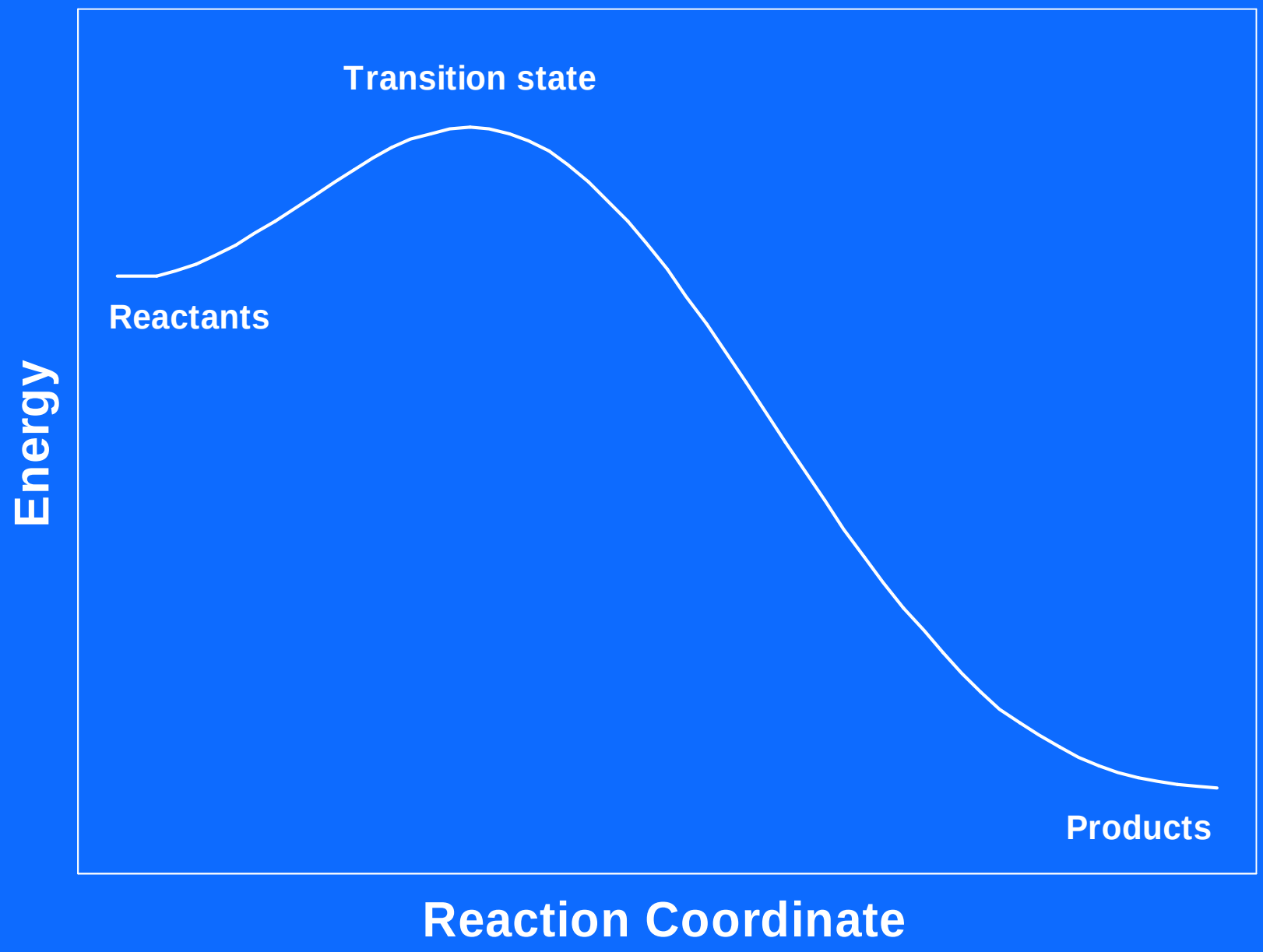
- Calculate a semi-empirical AM1 *Single Point Energy* on the “list” molecule, and include a Density surface with Potential property
- Display Properties and check the Dipole option
- Animate!
- Stop the animation long enough to turn off the dipole and turn on the surface, then animate again!

We’re not done yet!

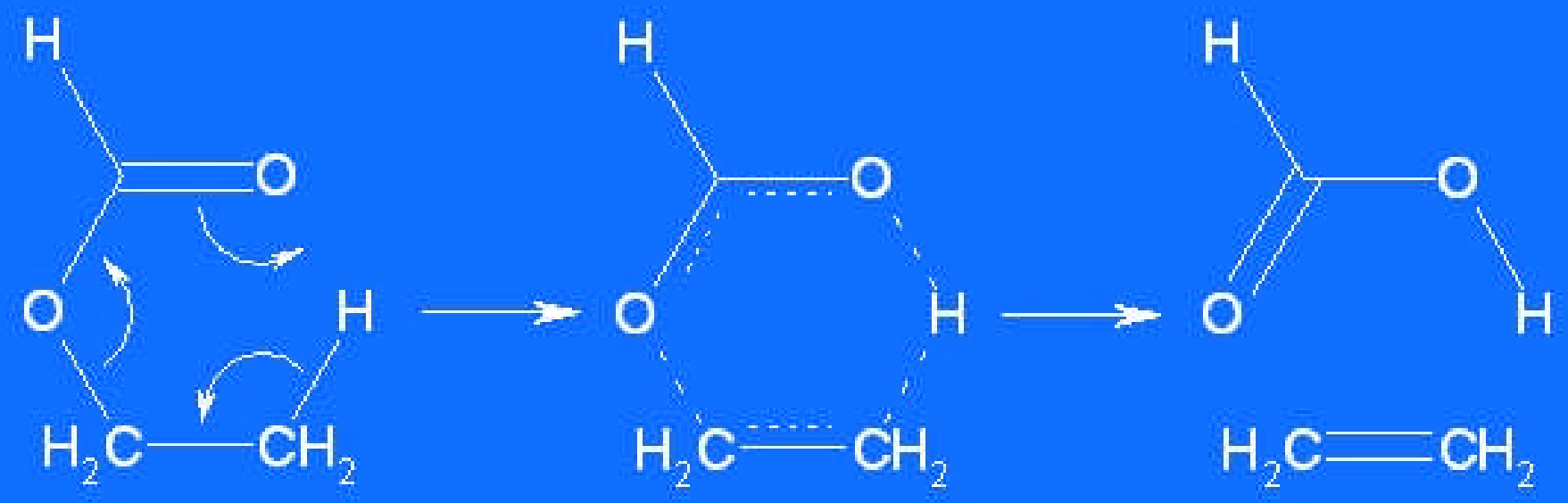
- Stop the animation and turn off the surface
- Open the Display Spreadsheet
- Add a column with Energy as a property, then close the spreadsheet
- Choose Display Plot, and put Energy on the y axis
- Animate!

Modeling
Chemical Reactions

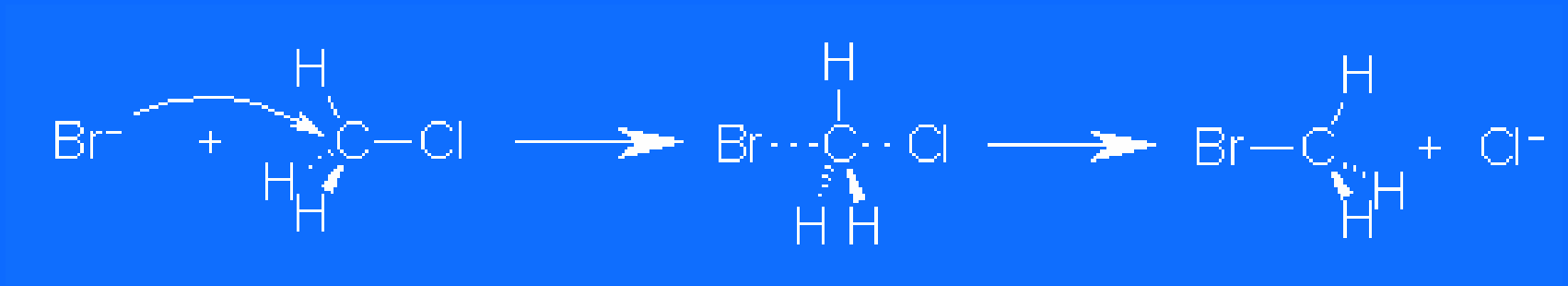
Potential energy diagrams describe chemical reactions



The pyrolysis of ethyl formate

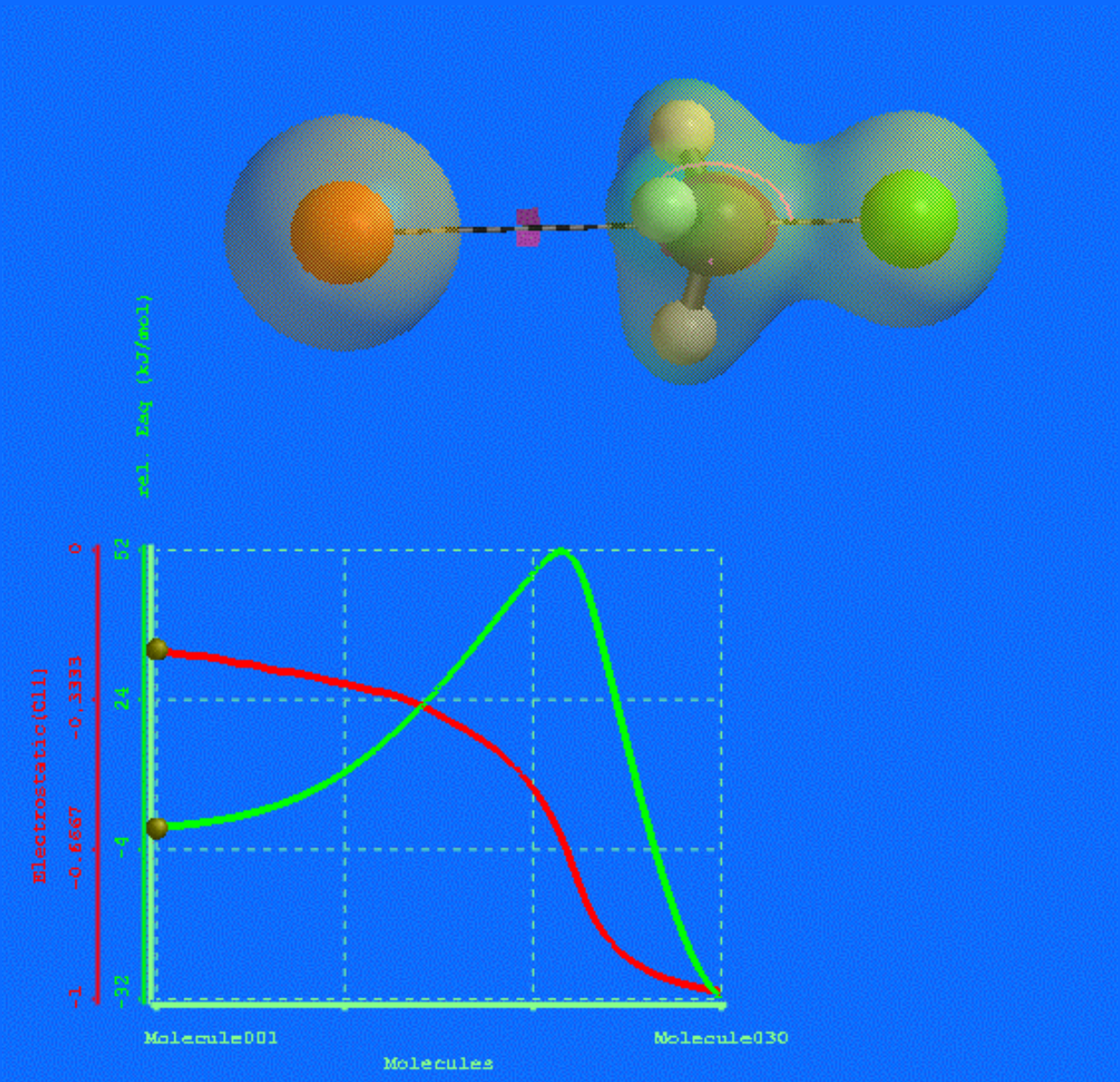


The S_N2 Reaction



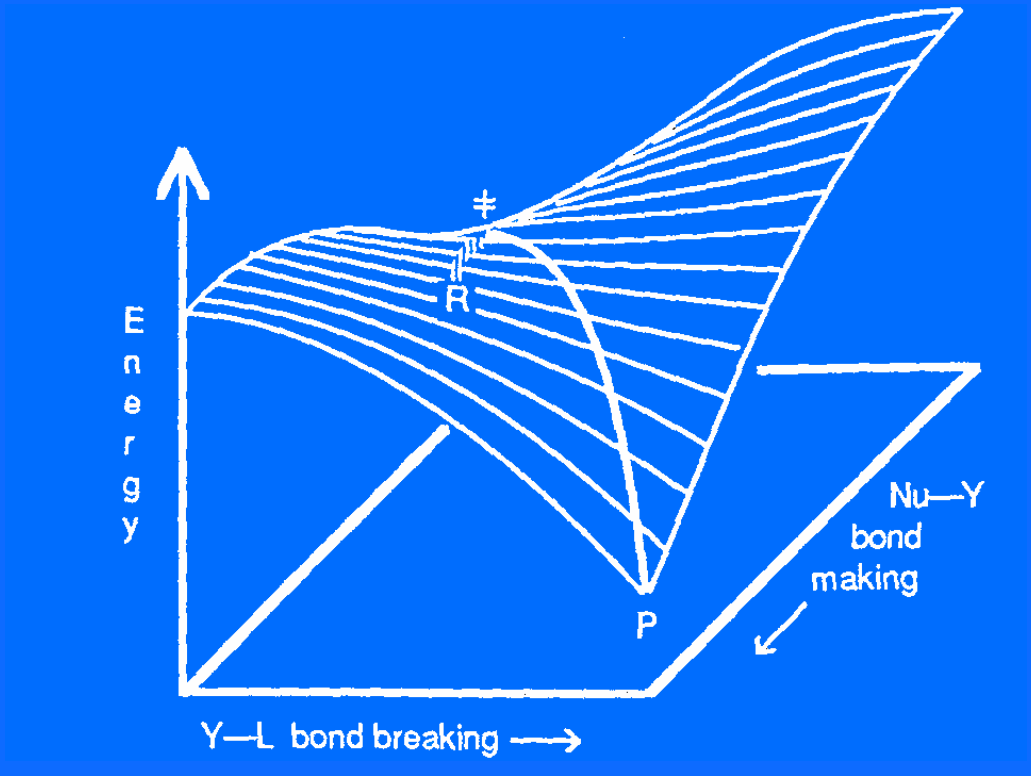
A bimolecular nucleophilic substitution reaction

The S_N2 Reaction



Potential Energy Surfaces

Remember potential energy surfaces are 3-dimensional. We normally think about and show to our students the 2-D slices shown in the notes. (reactants, transition states, intermediates, kinetics, thermodynamics)



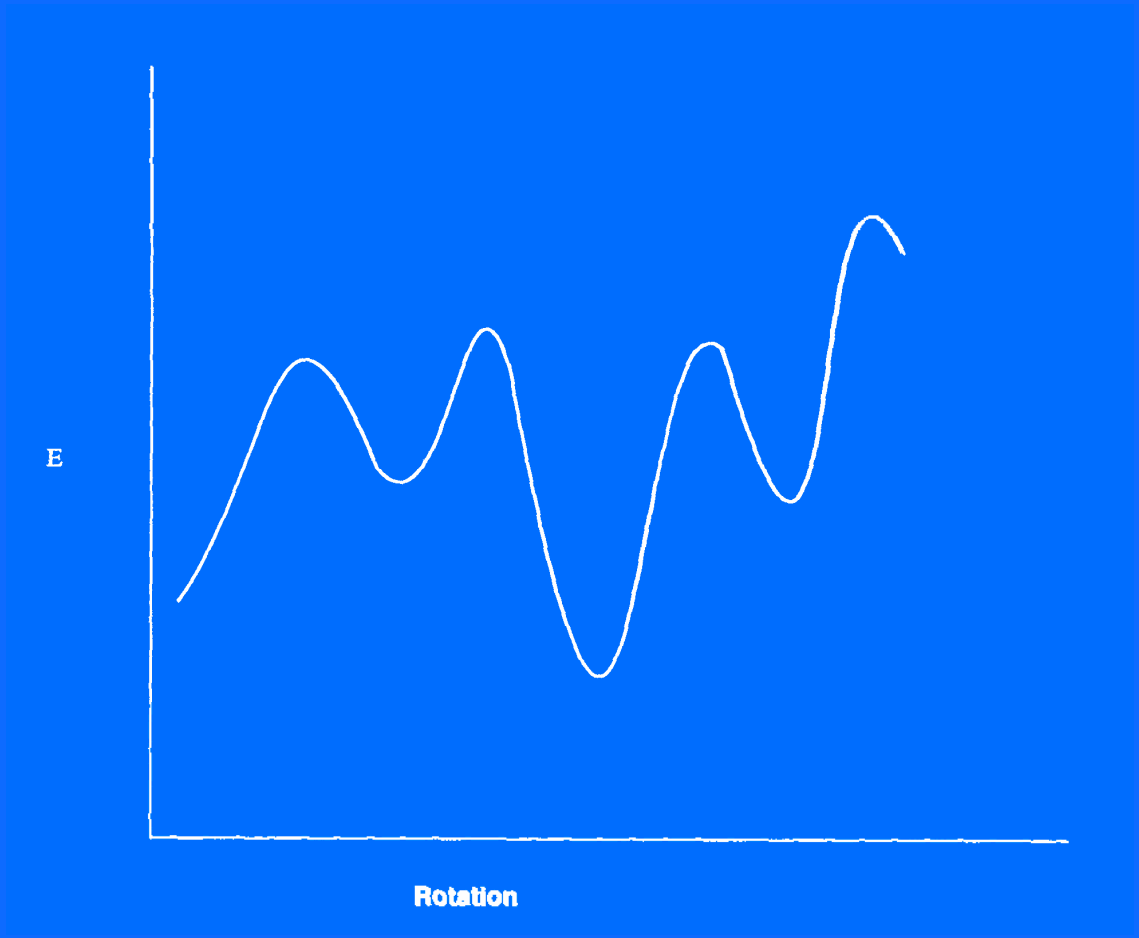
Pitfalls on the Potential Energy Surface

Problems

1. Local vs. Global Energy Minimum
2. “No-move” max

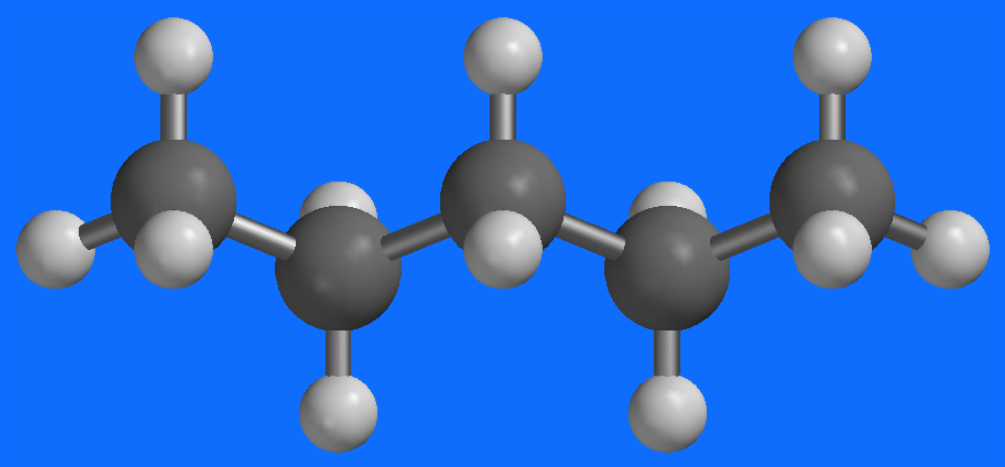
Solutions

1. Dynamics
2. Monte Carlo Methods



Conformations of Pentane

1. Construct pentane
2. Perform a Conformer Distribution calculation using Semi-Empirical AM1
3. Close the molecule, and open the Conformers molecule
4. Align the molecule set
5. Construct a spreadsheet of Relative Energy, and plot



How can we use these tools with our students ?

1. As a classroom demonstration tool

2. To generate PowerPoint or other overhead images and animations

3. As an adjunct to laboratory experiments

4. As a replacement for *some* laboratory experiences

5. As homework assignments

6. You fill in this one……..

Resources Available

The Molecular Modeling Workbook for Organic Chemistry

Molecular Modeling Supplements to textbooks
Wade, Bruice, Carey, McMurry, ……

Modeling within textbooks as images and problems
McMurry and Carey

The *Spartan Users* Group on Yahoo!

http://groups.yahoo.com/group/Spartan_Users/

- **Message Posting**
- **Live Chat**
- **Files**
- **Photos (orbital art?)**
- **Links**
- **Database**
- **Polls**
- **Calendar of Events**